Horizons Of Cancer Research

PROGRESS AND PROSPECTS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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Foreground: Recombinant DNA clone in *Escherichia coli* was extracted from the bacterial cells and mixed with a solution of cesium chloride and ethidium bromide dye. The sample was placed in an ultracentrifuge until a density gradient of cesium chloride formed in the tube. When ethidium bromide binds to DNA, it absorbs ultraviolet light and emits visible orange light, allowing researchers to identify the DNA bend and extract it for molecular biology studies. *Background:* Collage of photographs of a cisplatin crystal, at three different modifications.

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Acknowledgements

Executive Editor:
Patricia Newman Horm
Office of Cancer Communications,
National Cancer Institute
NCI Advisory Committee:
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*No longer at NCI
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Patient Profiles:
Jan Barkley, Hugh McIntosh, Cori Vanchieri,
Aubin Tyler, J. Beth Speyer
Sidebars and Captions:
Jan Barkley, Paula Kurtzweil, Cori Vanchieri,
Patricia Newman Horm
Glossary:
Cori Vanchieri

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The National Cancer Program owes its existence to the National Cancer Act of 1971. This legislation provided the National Cancer Institute with a mandate to "comprehensively and energetically exploit" new scientific leads in basic research. Specifically, the National Cancer Institute would further our understanding of the cancer process, and apply the results to improved methods of cancer detection, treatment, prevention and control.

Under the impetus of the National Cancer Act, public investment has grown remarkably over the past seventeen years, not only in cancer research but, more broadly, in all of biomedical research. The resulting pace and scope of scientific advance has been nothing short of breathtaking.

A large fraction of the scientific accomplishment is due to work sponsored by the National Cancer Institute (NCI). Indeed, many of the crowning achievements in the fields of molecular and cell biology, virology, immunology and molecular genetics have emerged from the research of the best and the brightest of our nation's scientists, supported by the National Cancer Program.

With respect to fundamental cancer research, progress has been so rapid that, by comparison, our understanding of neoplastic processes prior to 1970 can most fairly be described as primitive. At the time of the enactment of the National Cancer Act, we had little, if any, insight into the internal workings of the cancer cell. We knew very little about the disruption of control mechanisms responsible for aberrant neoplastic patterns of growth and differentiation or the biological and chemical processes responsible for invasion and metastasis. The molecular mechanisms that determined whether, and to what extent, cancer cells exhibited sensitivity or resistance to ionizing radiation or chemotherapeutic agents were as yet undiscovered.

The diagnosis of cancer rested upon histopathological and cytopathological criteria that were almost exclusively morphological. Specific and unambiguous tumor markers, and the capacity to identify particular molecular abnormalities in human tumor samples, were essentially nonexistent.

Scientific Advances Since 1971

The advances in the basic biomedical sciences of the past seventeen years have provided us with a wealth of understanding, a depth of insight, and an armamentarium of scientific and technological capacities that were unimaginable in 1970. Cancer scientists can now probe deeply into the innermost workings of the cancer cell. They can recognize and define with confidence an impressive and rapidly expanding array of specific abnormalities that have transformed our understanding of the cancer process.

The discovery and exploitation of highly specific enzymes that can cut the genetic material—DNA—at precisely defined locations, reattach their ends, and permit their reinsertion and continuous propagation in other living cells, have made many advances in knowledge possible. Scientists can now recognize and characterize abnormalities in chemical structure, chromosomal location, and regulation of expression of particular genes in specific forms of cancer cells.

These discoveries have also given birth to a biotechnology industry in which natural biological molecules of remarkable potency and specificity, normally present in man or animals in vanishingly small quantities, can be mass-produced for detailed physical, chemical, and biological study and potential therapeutic application.

From the results of this research

have emerged profound new understandings of the workings of normal and cancerous cells, the development of powerful techniques for cancer diagnosis, and the recognition of exciting new leads for cancer treatment and prevention.

Cancer Genetics. Progress in cancer genetics has been particularly remarkable. Much of the progress builds on the seminal discovery of genes in animal cancer viruses that are responsible for converting normal cells into cancer cells. Molecular biologists are recognizing and studying a growing number of so called "oncogenes," each of which appears to represent an abnormal or damaged version of a cellular gene that is ordinarily required for normal cell growth and tissue differentiation. These normal genes appear to be important, for example, during embryonic and fetal development, in the continuing orderly replenishment of body tissues, or in the healing of wounds.

The normal genes are fundamental to life itself, and in many instances they have been found to be highly conserved across vast stretches of evolution. Indeed, some specific human cancer genes have recognizable homologues in such primitive living forms as the fruit fly or baker's yeast!

The forms of genetic abnormality that have been recognized in human cancer are many, and include specific chemical mutation, gene breakage, rearrangement and translocation, gene duplication and gene deletion. In some cancer cells, genes that are not normally expressed after completion of fetal development are reactivated and produce strong signals of cell growth that are utterly inappropriate in the context of the mature organ or organism.

In other instances, genes that normally produce tiny quantities of critically important and powerful products under scrupulously regulated conditions behave as though they had become locked into a permanent "on" position, and continuously produce excess amounts of growth-stimulating molecules, or of other complex molecules that serve as specific receptors for the stimulators.

In yet other instances, genes that appear to suppress aberrant growth are damaged or lost, causing profound imbalances in intricate cellular regulatory networks, and leading to the breakdown of systems required for the modulation of normal cell growth and differentiation.

Cellular Communication. Impressive advances have also been made in deciphering substantial portions of the complex signaling mechanisms that nature has devised to permit orderly communications between and among cells. These mechanisms also facilitate appropriate responses within individual cells to signals that impact upon the outer limiting border of the cell, the cell membrane. We have come to recognize that each individual cell is an extraordinarily complex and delicately regulated entity with a remarkable system of internal communications. The control centers in the cell's interior are in constant communication with a myriad of external and internal stimuli.

In some forms of cancer, specific breakdowns in this communications system have been identified, providing new insights and suggesting exciting leads for specific chemical interventions.

A New Immunology. Progress in the fields of molecular immunology and immunogenetics has been particularly impressive. The development of monoclonal antibodies has provided scientists with powerful new tools. These tools permit the identification of specific molecular abnormalities in various forms of cancer, not only furthering scientific understanding, but providing entirely novel methods of cancer detection and exciting new strategies of cancer therapy.

For example, some monoclonal antibodies represent highly accurate homing devices that will recognize and attach to specific abnormal structures on some cancer cells, but not to normal cells nearby. It is possible to modify these antibodies by adding to them signaling molecules that can be detected by scanning devices, thus opening new avenues of sensitive cancer cell detection. Research is under way to use these molecules in treatment as well, by depositing highly toxic or radioactive chemicals with great precision on the surfaces of target cancer cells, to inactivate or destroy them.

Advances in immunology have also afforded progressively deeper levels of understanding of the enormous complexity of the human immune system and of the diversity of specific molecules and mechanisms. These signals enable the immune response to identify and destroy foreign elements—whether they be pathogenic bacteria, viruses or abnormal cells like tumor cells.

These advances, in turn, combined with recombinant DNA technology, have permitted scientists to prepare, in abundant quantity, certain of these immune molecules that are normally present only in trace amounts. Scientists now are exploring their utility as therapeutic agents to stimulate or enhance the cancer patient's own natural immune defense mechanisms to help fight the cancer.

This has resulted in an entirely novel form of cancer therapy, called biological therapy. Biologicals are now being added to such established modalities as surgery, radiation therapy and chemotherapy. Although still at a very early stage of development, some of the initial responses that

have been reported in applications of biological therapies to currently intractable cancers are extraordinarily promising and bode well for future development and exploitation of this entirely new mode of therapeutic intervention.

Threshold of a Golden Age. The successes achieved in biomedical research and the progressive accumulation of insight into human biology and pathology have generated a treasure of new ideas for improving risk identification, diagnosis and patient care. Never before in the history of medicine have creative strategies been so abundant and opportunities so available. Yet, although present optimism is high, we believe that the explosion of new information during the past seventeen years has brought us only to the threshold of a new era that will constitute a "golden age" for biology and for medicine.

Applying New Knowledge

The National Cancer Act of 1971 provided for the NCI to establish and expand mechanisms that permitted a coordinated, intensive approach to the cancer problem. The seventeen-year investment has resulted in a nationwide network of cancer centers, trained cancer physicians, an expanded clinical trials program, the cancer prevention and control program, and a variety of cooperative group and community outreach programs, like the Community Clinical Oncology Program, that enable community physicians to participate actively in research. The nationwide Cancer Information Service and Physicians Data Query, a computerized physician-oriented data base, bring the latest findings to patients, their families, and their physicians. The Statistics, Epidemiology, and End Results Program (SEER), established in 1973, continuously gathers information on new cases of cancer, deaths, and survival for more than 10 percent of the United States population.

Reducing Cancer Deaths. The objective of the National Cancer Act was to give the NCI the ability to be innovative, effective, and responsive in addressing the cancer problems in this country. As part of a continuing assessment of progress, the NCI has set a goal to cut the cancer death rate in half by the Year 2000. It is an effort to substantially reduce the impact of cancer in American life through smoking reduction, dietary changes, increased awareness and use of methods to detect cancer early, and enhancement of access to state-of-the-art treatment. But setting a goal is only the first step. Meeting it will require the coordinated and enthusiastic commitment of a wide array of governmental and private organizations all working together. It will also require that each of us accepts responsibility for the quality of our own life and steps forward to join this battle to reduce the cancer burden in our society.

The time from now to the Year 2000 is only twelve years—admittedly a very short interval; and the Goal for the Year 2000 is ambitious and bold. However, the innovations and accomplishments of the past seventeen years have given us hope and have led to the impetus of the present. Although setting a difficult goal carries a risk that the goal may not be achieved, recent history proves that a very great deal can be accomplished in a very short time.

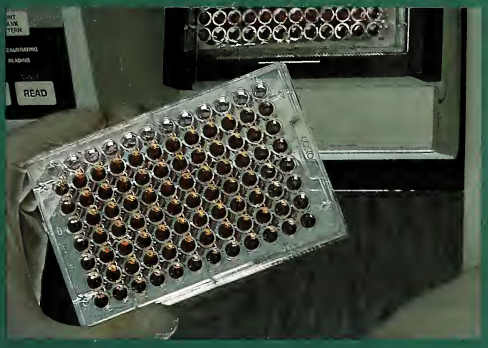
Reporting Progress. The National Cancer Advisory Board (NCAB), a presidentially appointed body charged with advising and assisting the federal cancer effort, is publishing this volume to provide insight into some of the substantial progress that has been made since 1971, to examine how this progress affects the lives of people every day, and to show how this knowledge has expanded the horizons of cancer medicine and cancer control. Today, as never before, the American public can look forward to further improvements that have been fueled by the advances of the 1970s and the 1980s.

It is not possible to attempt to more than sample the advances of the past seventeen years. Accordingly, we have selected illuminating examples of the robustness of cancer research and of how the reinvigorated commitment to basic research is steadily paying rich dividends to mankind.

In so doing, we shall show to some extent how research works—how seminal discoveries evolve incrementally from research clues, collected and collated over many years or decades. We shall show how the science of cancer prevention has emerged during the 1980s, generated from animal and other laboratory findings into finely-tuned prospective studies on novel chemopreventative strategies. And we shall describe how educational efforts are changing public perceptions about cancer by improving quality of life and reducing cancer risk.

At a time when our nation and the world continue to be transformed by stunning advances and ever more penetrating insights in biomedical knowledge, we can all take satisfaction in the accomplishments of the National Cancer Program and anticipate a rich harvest of future benefits from our sustained efforts in cancer research.

BASIC RESEARCH



"You can't go to a cancer research meeting these days without finding many people in a state of great exhilaration," says Dr. Janet Rowley, an expert on cancer genetics at the University of Chicago's Beverley E. Duchossis Cancer Research Center.

The fervor stems from a number of rapid-fire discoveries in the past ten years that pinpoint flaws at specific chromosomal sites as the cause of many cancers. These genes seem to govern cell growth and foster cancer development when they are switched "on" or "off" at the wrong times.

Scientists have suspected for decades that the root of a cancer cell's wayward behavior lies in the genetic machinery of the cell.

"In the past few years, five different cancer research areas — viruses, oncogenes, growth factors, growth regulation, and chemical carcinogenesis — have all come together," says Dr. George Vande Woude, of the NCI-Frederick Cancer Research Facility in Frederick, Maryland. "Their common language is the genes that are the molecular basis of cancer."

Tracing Cancer To Flawed And Wayward Genes

By Margie Patlak

ancer patients deal not only with the medical realities of a diagnosis of cancer, but with gnawing questions like, "Why did it happen to me?" and, "Where did it come from?" With time, they may worry about whether other family members are at risk. Young people with cancer wonder if they will ever be able to have children, and whether their children might inherit a risk of cancer. Some of the remarkable scientific advances of the last seventeen years in basic cancer research begin to answer some of these questions. Thanks to advances in molecular biology, scientists are pinpointing the kinds of changes that signal the development of many forms of cancer.

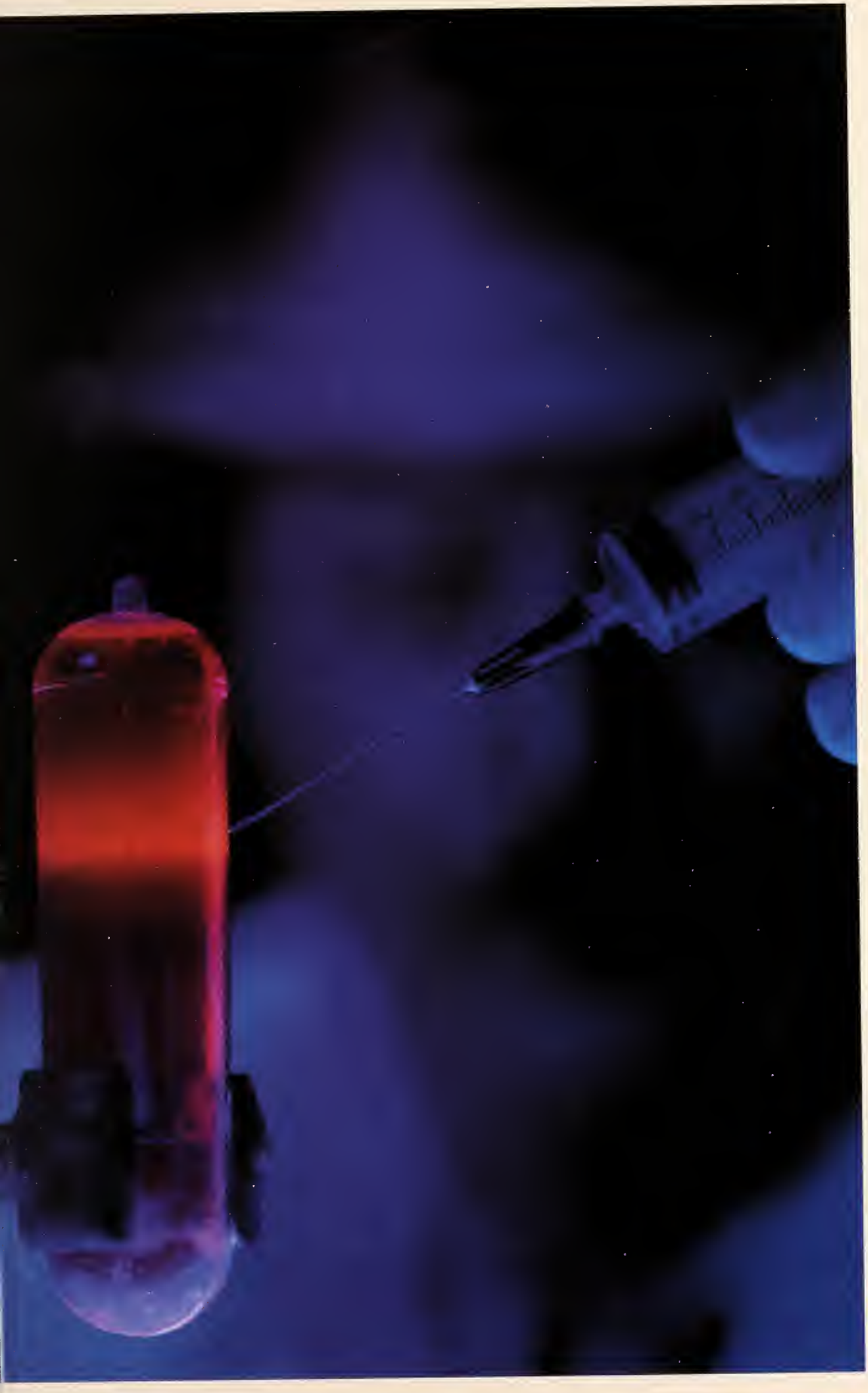
"It's a very exciting time," says Dr. Alfred G. Knudson, an expert in cancer genetics at the Fox Chase Cancer Center in Philadelphia. "The genes that seem to cause cancer are being cloned at a number of centers, and soon we'll understand how they work."

When a cell divides, it carefully copies its genes and distributes the copies to offspring cells. Although errors in copying occur only rarely, about once in every million cell divisions, they can have profound effects.

If the mistake occurs in the cells that form body tissues or organs, medical problems, including cancer, can result. If it occurs in developing sperm and egg cells, the error may be passed on to the patient's children.

For years, scientists have observed that some families have more cancer than others. Even in noninherited cancers, they have seen a variety of genetic changes in the cancer cells.

About 50 of the more than 120 different types of cancer occasionally have shown some



DNA, which is visible in the test tube, carries instructions that determine how each molecule in a living organism will function. Using a array of techniques to penetrate DNA's secrets, scientists are exploring fundamental life processes as well as diseases such as cancer.

type of familial clustering. However, "cancer families" in which many members develop one or more types of cancer, are uncommon.

Most cancers occur randomly in the human population, presumably due to genetic changes caused by environmental exposures. Scientists now believe that genetic changes, inherited or acquired, are the basis of cancer.

One of the first cancers recognized as hereditary was familial retinoblastoma, a rare eye cancer that develops in children and often affects both eyes. As many as 40 percent of retinoblastomas are considered hereditary, meaning that the cancer risk can be passed on to the patient's children. Yet, only about 5 percent of the cases in the United States each year occur in children with a known family history of the disease.

Most retinoblastomas are not inherited. They occur randomly in the population and commonly affect only one eye. Overall, about 5 of every 100,000 children develop retinoblastoma between birth and age seven.

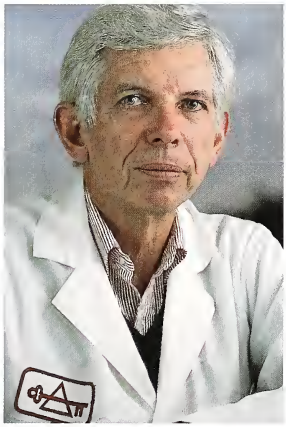
More than fifteen years ago, Knudson noticed that children under age one who developed retinoblastoma frequently suffered from the more aggressive disease, with cancers in both eyes.

Knudson was impressed that a child from a family with retinoblastoma, with a 50 percent chance of inheriting the disease, could have the cancer in one eye, both, or neither. "This implied to me that having a familial predisposition wasn't enough to get the cancer—something else had to happen to spur cancer development," Knudson says.

"We have two copies of every gene in most of our cells. The simplest explanation for retinoblastoma would involve knocking out both copies of the gene," Knudson explains.

In the 1950s and 1960s, scientists explained the long time period needed for cancer development as evidence that at least two separate events must occur in the cell before it converts to a cancer cell.

In the early 1970s, Knudson statistically analyzed the patterns of occurrence of retino-



Dr. Alfred G. Knudson was honored in 1988 by the General Motors Cancer Research Foundation for his research to explain how some childhood cancers can result from genetic mistakes.

The Genes of Retinoblastoma

Retinoblastoma, a rare eye cancer of childhood, can be either hereditary or spontaneous. Both forms are caused by the loss of function of genes carried on chromosome 13. Cancer does not arise as long as one copy of chromosome 13 is normal. In the hereditary form (left), the newborn has a copy of chromosome 13 that has missing or damaged genes in the region associated with retinoblastoma. A healthy newborn (right) has two normal copies of the chromosome.

As retinal cells divide during the first nine months of life, random errors cause gene damage in about one of every million cell divisions. In hereditary retinoblastoma, this error may cause tumor growth.

It is very rare that random errors will occur in both copies of the retinoblastoma gene in one cell. Nonetheless, within the first few years of life, in a small number of healthy children, mutations in both genes of a single eye cell cause the cancer. Since their other cells remain unaffected, children with the spontaneous disease, unlike those with the inherited form, will not pass retinoblastoma on to their offspring.

The early, middle, and late stages of retinoblastoma growth can be seen in the photos below, in the eyes of three children. The tumor appears as a white, foamy mass in the pupil. Depending on the stage of disease, treatment options include surgery, cryosurgery or radiation.

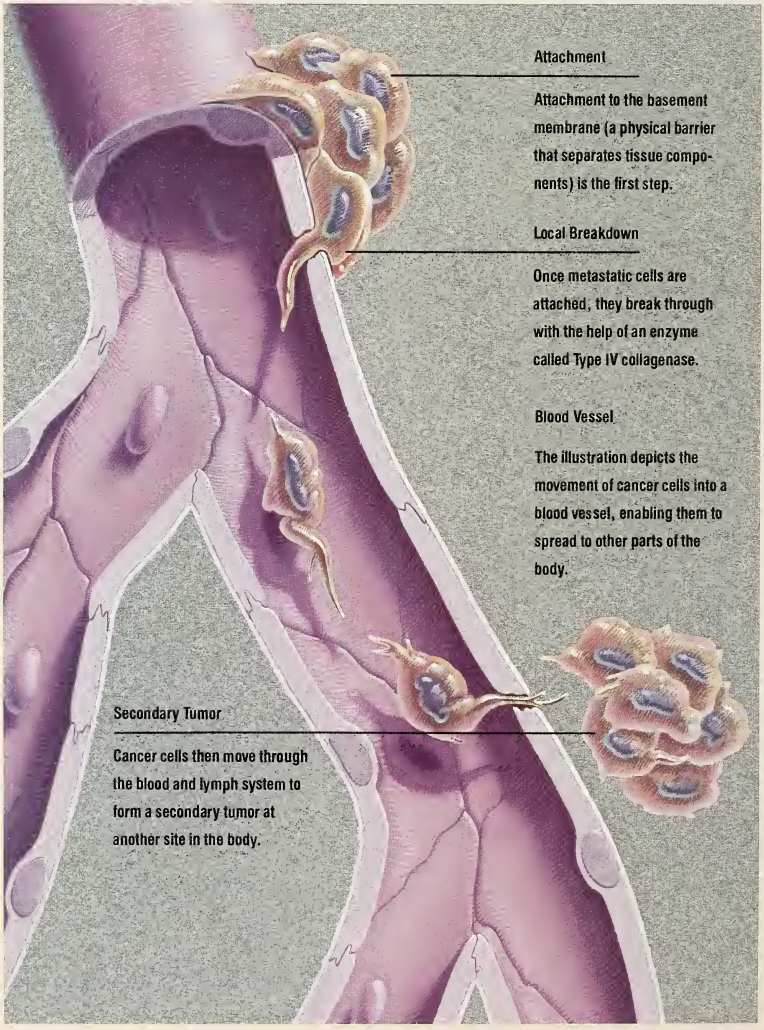
Locomotion is integral to the entire process of metastasis. Scientists have identified a protein, named autocrine motility factor, that causes cancer cells to grow arms or pseudopodia, enabling them to begin to move to other parts of the body.

How Cancer Spreads

Cancer has two distinctive characteristics: disorderly, abnormal cell division, and metastasis, a progressive spread to other parts of the body.

Some cancers spread more aggressively than others. Scientists are locating genes, enzymes and other proteins that help cancer cells break down the linings of organs and capillaries and move to other locations in the body.

Scientists are learning more about the genes and biochemical pathways that govern metastasis, and how to use that knowledge to block metastasis. For example, studies are under way to see if antibodies against autocrine motility factor might keep cancer cells from migrating.



blastoma and proposed his two-hit hypothesis, which suggested that as few as two gene changes could be enough for the cancer to develop. He showed that the hereditary form of the disease occurred in a statistical pattern consistent with an initial mutation occurring in an egg or sperm cell. Retinal cells are continually dividing as the retina develops during pregnancy and early infancy. If, at some point, the second, normal copy of the gene were damaged, cancer could form.

Knudson hypothesized that the spontaneous retinal cancers in people without a hereditary disposition occurred when two chance events damaged both genes in the same retinal cell—a very rare coincidence in the general population.

He then looked at other childhood tumors, including those of the kidney and nervous system, and proposed that they also fit the two-hit scenario.

In the 1970s and early 1980s, newly developed techniques—the products of rapid developments in cell and molecular biology, let researchers study DNA in greater detail and develop ways to examine cells for specific regions that might be responsible for disease.

One advance enabled scientists to more clearly examine the organization of human chromosomes, structures in the nucleus of the cell that contain tightly packed bundles of genes. Using dyes, the scientists found that because of the unique banding pattern of each chromosome, specific segments could be numbered for identification.

Banding studies showed that most patients with retinoblastoma, those with the nonhereditary form of the disease, have two normal copies of chromosome 13 in their blood cells, but their cancer cells may be missing the 13q14 region.

In rare retinoblastoma patients, those with mental retardation or other birth defects, even normal blood cells turned out to be missing the 13q14 segment.

Then, scientists discovered that another gene, which directs the production of a readily identifiable enzyme, was also located on 13q14.

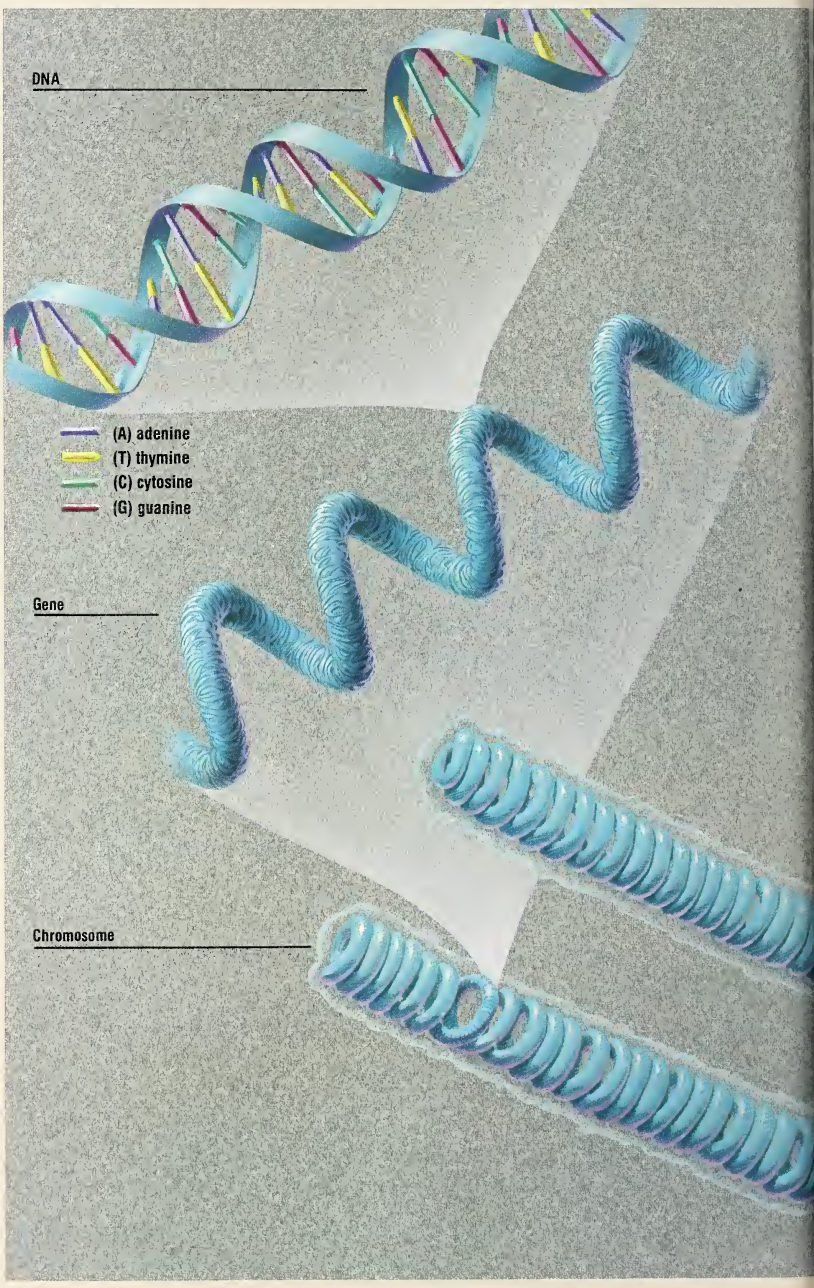
Webster K. Cavenee developed probes that identified the chromosomal segment that is missing in retinoblastoma, providing evidence from molecular genetics that the two-hit hypothesis was correct.

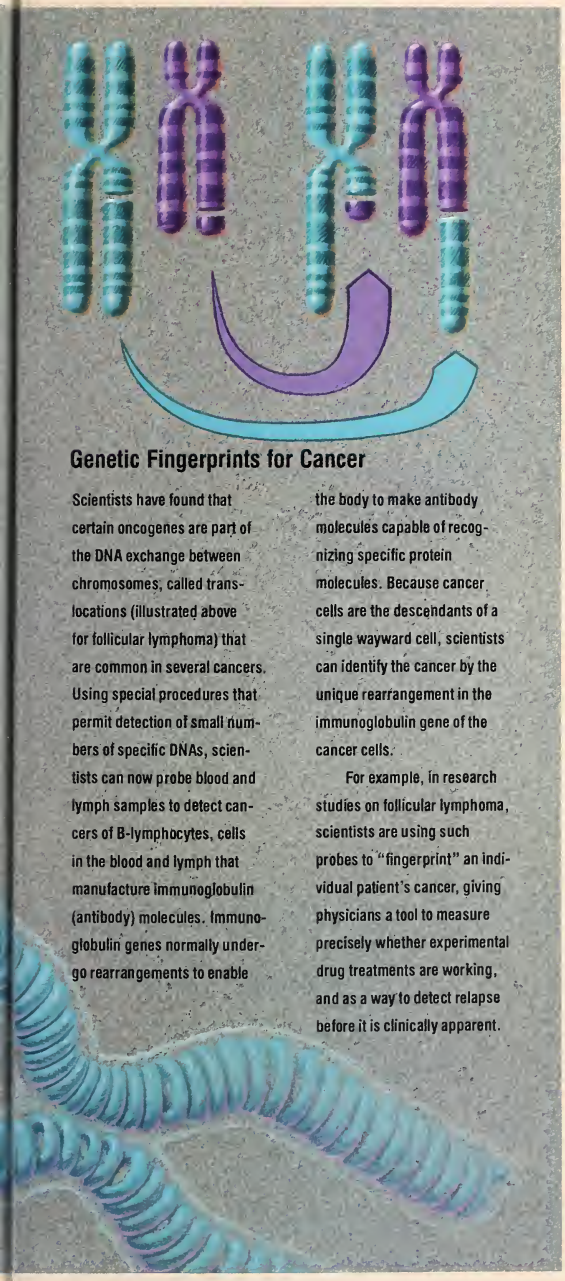
How Cells Package Genetic Information

Several billion nucleotides are packed into the nucleus of each human cell in a precise linear order. There are four types of nucleotides, adenine (A), thymine (T), guanine (G), and cytosine(C), ordered precisely to encode all the genetic information of an individual in DNA (deoxyribonucleic acid). In the laboratory, scientists now selectively break down DNA into smaller segments, determine the precise order of the nucleotides and predict the product.

Genes are segments of DNA that encode a specific protein product. Each gene has two parts, a portion that is copied into RNA, the chemical that carries out the gene's instructions, and a "switch" portion that controls this copying process. Genes are switched "on" or "off" in different tissues at different times.

Each individual cell carries about 50,000 genes, packaged in the cell nucleus into tiny bundles called chromosomes. Except for genes carried by egg and sperm cells, which have only one copy of each gene (to allow the gene mixing that makes each person unique), every cell has two copies, one from each parent. When a cell divides, it must correctly copy every gene and apportion the chromosomes to the daughter cells.





Genetic Fingerprints for Cancer

Scientists have found that certain oncogenes are part of the DNA exchange between chromosomes, called translocations (illustrated above for follicular lymphoma) that are common in several cancers. Using special procedures that permit detection of small numbers of specific DNAs, scientists can now probe blood and lymph samples to detect cancers of B-lymphocytes, cells in the blood and lymph that manufacture immunoglobulin (antibody) molecules. Immunoglobulin genes normally undergo rearrangements to enable the body to make antibody molecules capable of recognizing specific protein molecules. Because cancer cells are the descendants of a single wayward cell, scientists can identify the cancer by the unique rearrangement in the immunoglobulin gene of the cancer cells.

For example, in research studies on follicular lymphoma, scientists are using such probes to "fingerprint" an individual patient's cancer, giving physicians a tool to measure precisely whether experimental drug treatments are working, and as a way to detect relapse before it is clinically apparent.

Gene Changes and Cancer Diagnosis

The cancers of thousands of patients are being diagnosed with increased precision by laboratory pathologists, thanks to tests for unique markers that only a few years ago were the exclusive realm of molecular geneticists.

For years, pathologists have routinely tested many patients' leukemia and lymphoma cells for a variety of chromosomal abnormalities. These analyses were made possible in the 1970s by the advent of a new technique, chromosome banding, that enabled scientists to visualize chromosomes clearly.

Some abnormalities became diagnostic, such as in chronic myelogenous leukemia, where appearance of an odd chromosome named the Philadelphia chromosome identifies this cancer. As a result of banding, scientists learned that the Philadelphia chromosome was actually chromosome 22 with a translocation from chromosome 9. In the 1980s, scientists found that a specific gene named c-*abl* was part of the translocated chromosome segment on chromosome 22, where it fused with another gene and made an abnormal product.

Another example is Burkitt's lymphoma, a rare childhood cancer of immune system cells with a characteristic chromosomal translocation. Another specific gene, named c-*myc*, in the 1970s was detected near the translocation breakpoint on chromosome 8, next to a gene for antibody production. Presumably, the *myc* gene is under the same activation control as the antibody gene, and its protein product drives the cell through repeated rounds of cell division. C-*myc* also appears in rearrangements of the chromosomes of lymphoma cells from AIDS patients.

A gene named *bcl-2* by its discoverer, Dr. Carlo Croce of the Wistar Institute, moves from chromosome 18 during a translocation between chromosomes 14 and 18 in follicular lymphoma. In this, the most common lymphoma affecting adults over age forty, the translocation occurs in more than 90 percent of patients. The *bcl-2* gene moves to chromosome 14, where it sits next to another of the antibody-producing genes.

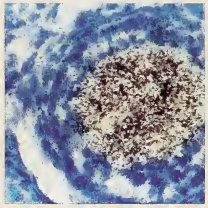
By examining the cells of people within retinoblastoma families, scientists saw that the cancer occurred in family members with a particular enzyme variant, confirming that the predisposing gene was located in that region.

In 1983, while at the University of Utah, Webster K. Cavenee made a series of special probes for precise pieces of the 13q14 region of the chromosome. In collaboration with other scientists in the United States and Canada, he looked for a pattern of hereditary transmission from parents with retinoblastoma to their children. By comparing the patients' normal and cancer cells, he showed that the cancer cells had lost the 13q14 region from the unaffected parent and sometimes instead had duplicate copies of chromosome 13 inherited from the parent that had retinoblastoma as a child. The cancer cells had two mistakes in 13q14, one on each chromosome 13. As a result, no normal copy of the retinal gene remained, allowing the disease to occur.

Several researchers in laboratories throughout the world then began a quest to isolate and clone the specific gene that is missing in retinoblastoma cells. During 1986, researchers at the Massachusetts Eye and Ear Infirmary, led by Dr. Thaddeus Dryja, reported finding a probe within the region of the retinoblastoma gene. Then, Dr. Stephen Friend and coworkers in Dr. Robert Weinberg's laboratory at the Whitehead Institute for Biomedical Research, in collaboration with Dryja's group, cloned the putative retinoblastoma gene. Soon, in California, Wen-Hwa Lee of the University of California at San Diego and Yuen Kai T. Fung of the University of Southern California confirmed and extended these findings.

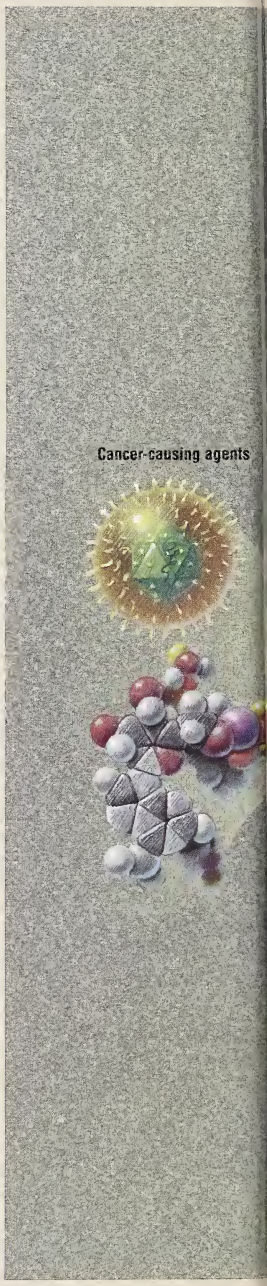
By isolating the gene and studying the precise order of nucleotides it contains, scientists expect to gain unprecedented insights into how normal genes work and how loss of gene functions leads to some cancers.

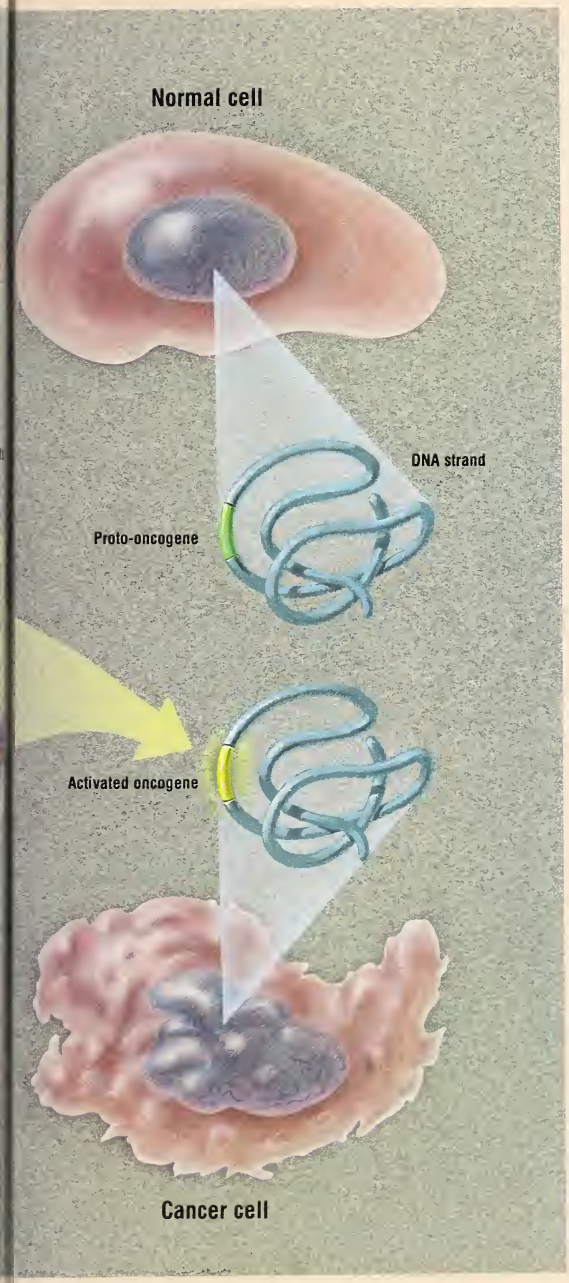
Now director of the Ludwig Institute for Cancer Research in Montreal, Cavenee has used



A technique called *in situ* hybridization shows whether a gene is actively expressed in cells, and also provides clues to the gene's function. This technique has helped identify activated oncogenes in cancer cells, and their normal counterparts in normal cells, in many different species. In this photograph, a labeled DNA segment (a known oncogene) has been put into a mouse oocyte, a cell that develops into a mature egg cell. The labeled DNA has paired with (or hybridized to) multiple copies of RNA in the mouse oocyte. The presence of this RNA (shown here as black dots inside the nucleus of the immature cell) shows that the normal cellular counterpart of the oncogene is active, suggesting that it is critical for normal germ cell development.

Photo Credit: Basic Research Laboratory, Frederick Cancer Research Facility.





What is an Oncogene?

An oncogene is a specific gene that participates in changing a normal cell into a cancer cell. It is a variant of a normal cell gene.

The first clues to oncogenes came from research on the life cycle of retroviruses, a family of viruses that can cause leukemias and solid tumors. These viruses have been found in reptiles, birds, and mammals, including humans.

During the 1970s, scientists used the new techniques provided by molecular biology to examine the genes in these viruses. They found that some retroviruses contained genes that gave the viruses the ability to stimulate abnormal cell growth, and they named those genes oncogenes.

They also found normal genes that were structurally similar to oncogenes. Certain retroviruses, it turned out, had captured genes from normal cells and had substituted these cellular genes for some of their own genetic information.

Within the retrovirus, the oncogenes are mutated and can spread to new cells by infection. In the normal cell, these genes appear to regulate and influence normal cell growth and cell divison.

Because of this research, scientists are developing greater understanding of normal as well as cancerous cell growth. Some of the more than 50 known oncogenes encode proteins called growth factors that encourage cells to divide, and some make proteins that transmit growth signals inside the cell. Still other gene products stay inside the nucleus of the cell, where they can bind to DNA and control critical processes.

Dr. Michael H. Wigler of the Cold Spring Harbor Laboratory on Long Island has been a leader in research on DNA. He showed that the primitive yeast organism contains a gene needed for normal growth that has structural similarity to a gene in human DNA.

Says Wigler, "If you knock out the gene in yeast and replace it with the human gene, the yeast will grow and divide extremely well. But if you mutate it and insert it into mouse cells, you can transform the mouse cells, causing loss of growth control."

his probes to predict, prenatally, which infants from retinoblastoma families are likely to develop the disease. One infant that Cavenee predicted would develop retinoblastoma was examined at a few weeks of age and found to have two tumors in each eye. Prompt treatment with radiation saved the infant's eyes and sight.

In research studies, other scientists are now using probes like Cavenee's and Friend's in families with retinoblastoma to help identify family members who have inherited a susceptibility to the disease.

The probes also are being used to study survivors of hereditary retinoblastoma, who have a 15 percent chance of developing other cancers, usually osteosarcoma, a bone cancer. Using his molecular probes, Cavenee and coworkers showed that in two of three retinoblastoma patients who subsequently developed osteosarcoma, the osteosarcoma cells had alterations in the 13q14 region of chromosome 13. Osteosarcoma cells from three of four patients with the spontaneous form of the disease (that is, no family history of retinoblastoma) also had the defect. Because the defect was found in the cancer cells of one of the patients prior to cancer drug treatment, the scientists believe that, as in retinoblastoma, the defective region of the chromosome was responsible for both the inherited and spontaneous osteosarcomas.

Other research is looking at other cancers to see if cancer cells show abnormalities in the region of chromosome 13 that is changed in retinoblastoma. Recent work by Friend and colleagues has shown deletions in patients who have never had retinoblastoma, but who have developed certain soft tissue sarcomas.

Cavenee and other scientists have looked for similar gene defects in other, more common, cancers. For example, Cavenee has found alterations on chromosome 13 in ductal breast cancer cells from premenopausal patients. He and other groups have reported a pattern of gene defects, similar to those seen in retinoblastoma, in patients with Wilms' tumor, a childhood kidney cancer, where the deletion occurs on chromosome 11.

At the Childrens Hospital of Los Angeles and the University of California at Irvine, Dr. Eric J. Stanbridge and coworkers have shown that introducing a single normal human chromosome 11 into laboratory grown Wilms' tumor cells, which are then injected into mice, curtails the ability of the cells to form tumors in the mice. The implication is that the normal chromosome 11 contains a region that, when missing, contributes to the development of cancer, and when present, helps prevent the development of the cancer.

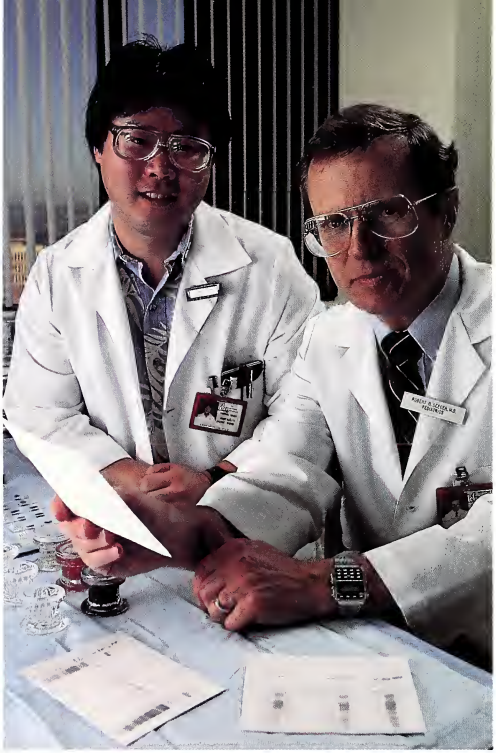
Certain other cancers of children, and other more common cancers of adults, are now being studied by other groups of scientists to see if missing or damaged areas of chromosomes can be identified.

A key finding by Sir Walter Bodmer and Dr. Ellen Solomon and their coworkers at London's Imperial Cancer Research Fund suggests that some colon cancers are due to two-hit mechanism involving an inherited or acquired mutation at a particular site on a chromosome. Their work stems from an individual case report: a portion of chromosome 5 was missing in a patient with familial adenomatous polyposis, a rare hereditary condition that shows up in adolescents. In this disease, the large intestine is carpeted with hundreds of small growths called polyps, and these patients are at high risk of developing colon cancer.

Bodmer and colleagues, using a probe for the missing region of chromosome 5, were able to trace the disease in the polyposis families, demonstrating that the predisposing gene lies in that region. Using another probe for the same chromosome 5 segment, Solomon and her coworkers showed that the segment is missing in the cancer cells of some patients with common, nonhereditary forms of colon cancer. This suggests that cancer occurred as a result of loss of a gene needed for normal cell growth regulation.

While some cancers are caused by damaged or missing genes, other cancers appear to be

Dr. Eric Stanbridge (left) and coworkers have studied the role of specific genes in stimulating and inhibiting the growth of cancer cells in mice.



Dr. Robert C. Seeger (right), and his colleagues use aggressive therapy in neuroblastoma patients whose cancer cells have 10 or more copies of an oncogene.

prompted or rendered more aggressive by the presence of altered or activated genes called oncogenes. Originally discovered in the 1970s in animal cancer viruses, oncogenes have been shown to play a role in a wide range of human cancers, including those of the breast, colon, lung, bladder, nervous system and blood.

In the past several years, scientists have begun to study the role of normal genes related to oncogenes in cell division or differentiation. When altered, these normal genes may play a role in cancer.

Although scientists have yet to learn exactly how oncogenes spur the growth of cancers, their presence in cancer cells may already be useful in predicting which patients should have more aggressive cancer treatment.

"The key treatment issue for cancer is knowing how aggressive a tumor is," says Dr. Robert C. Seeger of the Jonsson Comprehensive Cancer Center, University of California at Los Angeles. "You don't want to overtreat someone and subject them to a risk of dying from complications of the treatment, but you also don't want to undertreat another patient with a particularly aggressive tumor. We try to identify the subset of patients who won't do well with conventional treatment and find something better for them."

Using a gene screening technique called Southern blotting, Seeger and his colleagues at the Children's Cancer Study Group in Los Angeles and Dr. Garrett M. Brodeur of the Washington University in St. Louis were the first to correlate the presence of excess copies of a particular oncogene in cancer cells with the stage of disease.

Cells usually have only two copies of each gene, one from each parent. But when Seeger and Brodeur looked at the cancer cells of children with neuroblastoma, a cancer of the nervous system, they found many of the cells had ten or more copies of an oncogene called *N-myc*. When the researchers compared the number of copies of *N-myc* in each patient's cancer cells with the progress of the patient,

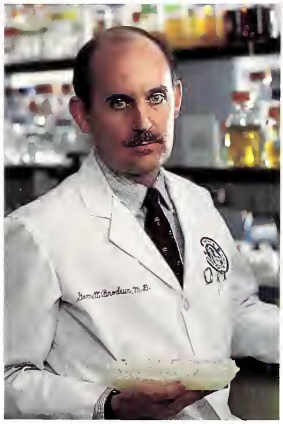
they found that the more copies of the gene, the more rapidly the cancer spread.

The researchers were quick to put these findings into practice. Seeger treats patients who have localized cancers and few or no excess copies of the gene with surgery, conventional chemotherapy, and radiation. But he treats patients who have ten or more copies of *N-myc*—even if their cancer has not spread—with chemotherapy and radiation so intense that it requires bone marrow transplants to restore their blood cells.

Since Seeger and Brodeur made the connection between excess copies of *N-myc* and poor prognosis, their colleague, Dr. Dennis J. Slamon of the University of California at Los Angeles has discovered the same relationship between copies of the oncogene *HER-2/neu/erB-2* and breast cancer. Although Slamon's data are still preliminary, he is encouraged by findings indicating that the more copies of the oncogene in the tumor cells, the more aggressive the cancer. If further studies support his initial findings, doctors may be able to predict which women are most likely to have a recurrence of breast cancer and should be treated with chemotherapy or radiation.

"Even if the *HER-2/neu/erB-2* oncogene doesn't pan out the way we'd like it to," Slamon says, "there are a number of other oncogenes that might prove more prognostic. There must be something going on at the level of the gene that can tell you why some people's cancers are more aggressive than others."

The discovery of such genes could not only refine prognosis, but foster more effective treatments for certain cancers. "If a gene product is important in a disease process, then drugs that block that molecule hold potential for therapy," Slamon says. Echoing Knudson, he adds, "These are exciting times."



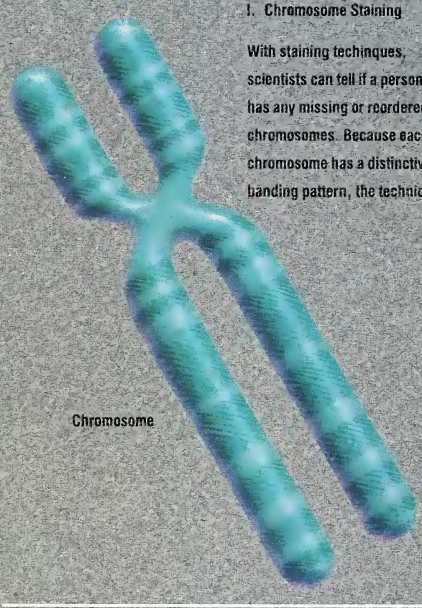
Dr. Garrett M. Brodeur developed oncogene probes and helped show the relationship between oncogene activity and stage of disease in neuroblastoma.

Pinpointing the Genes in Cancer

Scientists can now pinpoint some of the genes associated with cancer, thanks to techniques that allow them to tell chromosomes apart, detect genetic markers for disease susceptibility, and isolate specific genes.

In higher organisms such as humans, a single gene can span hundreds of thousands of bases; chromosomes have hundreds of millions of bases. The complete complement of human DNA comprises three billion base pairs in a precise order. To duplicate the genes and develop a more precise genetic map of human genes and chromosomes, scientists are using recombinant DNA techniques in yeast. Yeast can replicate millions of bases at one time, enough to copy large segments of human DNA. This type of research promises to help scientists understand better how genes are organized on chromosomes. The new insights promised by genetic analysis promise unprecedented progress in understanding diseases such as cancer.

Three Key Techniques



Chromosome

I. Chromosome Staining

With staining techinques, scientists can tell if a person has any missing or reordered chromosomes. Because each chromosome has a distinctive banding pattern, the technique distinguishes between different chromosomes or chromosome segments.

A fluorescent or radioactive dye is added to chromosomes. The dye creates light and dark patterns that identify individual chromosomes and missing, added or translocated segments. Individual bands also serve as markers for the positions of specific genes. Each band contains millions of precisely ordered pairs of bases, about 5 to 10 percent of the DNA in the chromosome.

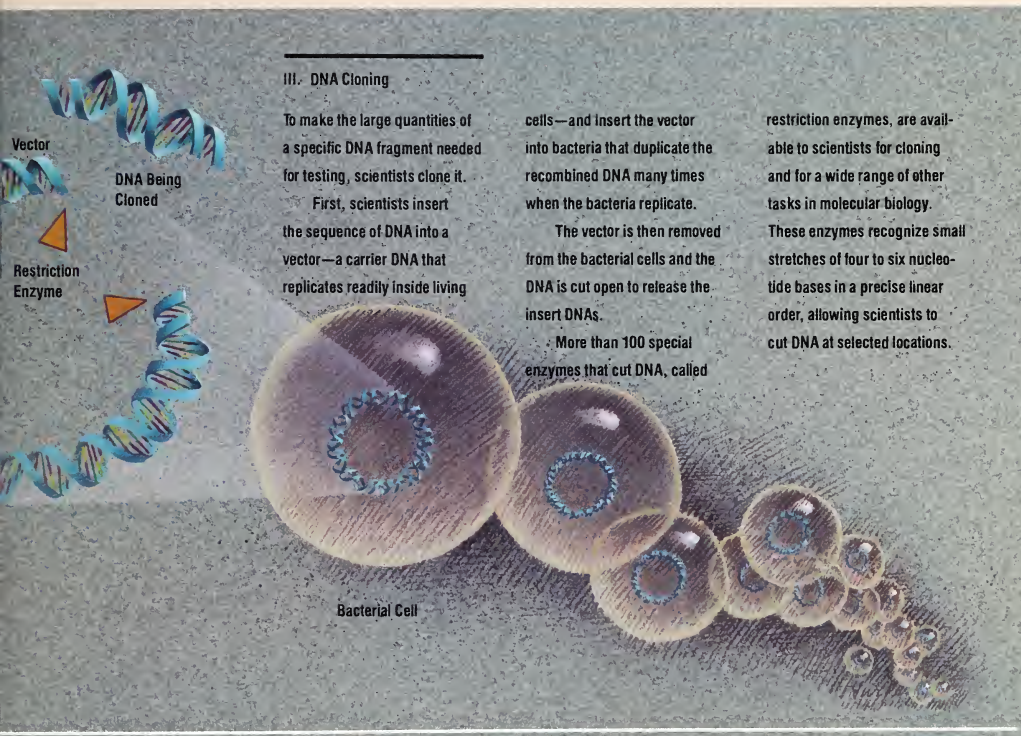
II. Inherited Markers

Two research strategies, when combined, tell scientists where defective genes are located in human DNA. They are: (1) a study of inheritance patterns in families with a specific cancer (such as retinoblastoma) appearing over two or more generations; and (2) sophisticated techniques that identify the precise order of the chemical subunits in DNA. Natural variations in this order, called polymorphisms, make each person unique.

The DNA of blood cells from family members are cut into fragments by restriction enzymes and are separated by size with a technique called a Southern blot. Variations that are inherited over several generations can be detected by comparing the DNA of family members.

in a family with inherited disease, a fragment with a particular DNA variation that is always inherited is a marker if its presence always coincides with disease occurrence. This molecular examination of inheritance is called "RFLP" an-

DNA



III. DNA Cloning

To make the large quantities of a specific DNA fragment needed for testing, scientists clone it.

First, scientists insert the sequence of DNA into a vector—a carrier DNA that replicates readily inside living cells—and insert the vector into bacteria that duplicate the recombined DNA many times when the bacteria replicate.

The vector is then removed from the bacterial cells and the DNA is cut open to release the insert DNAs.

More than 100 special enzymes that cut DNA, called restriction enzymes, are available to scientists for cloning and for a wide range of other tasks in molecular biology. These enzymes recognize small stretches of four to six nucleotide bases in a precise linear order, allowing scientists to cut DNA at selected locations.

chromosome is growing rapidly. The technology is also contributing to the development of maps of genetic markers on human chromosomes.

alysis, for restriction fragment length polymorphism. A RFLP, or DNA variation, helps identify disease risk if it is located on a chromosome near the gene believed responsible for an inherited disease.

RFLPs are potent diagnostic tools that can be used prenatally or soon after birth. The list of familial cancers (and a host of other inherited diseases) being linked with RFLPs to specific regions of a

TREATMENT

A relatively short era in medical history has ushered in remarkable innovations in therapy. Surgery has become more precise and less mutilating, while radiation therapy has grown more powerful as well as safer. Potent new drugs, including biologicals, hormone-like chemicals secreted by body cells, and extracts of exotic plants, are being used in ingenious combinations designed to inflict great damage on cancer cells while sparing normal tissues.

Such developments, typically the outgrowth of laboratory research and always the subject of thorough clinical testing, bear testimony to a lively interplay between the laboratory bench and the patient bedside. Along with impressive advances in diagnostic methods, these new therapies—which have significantly improved survival for substantial numbers of cancer patients, and effected cures for many—are being made available to Americans in communities throughout the country.

Adjuvant Chemotherapy: A New Treatment Approach Proves Itself

By Hugh McIntosh

octor Barnett Rosenberg would have been happy if the mouse tumors he was treating only grew to half the size of the untreated ones in his control group. That would mean the yellow crystal compound he was testing possessed "significant" potency against cancer.

When he examined them eight days later, Rosenberg found, to his delight, that the test tumors weighed barely 2 milligrams. They were, in fact, 250 times smaller than the control tumors.

Nearly two decades after this discovery of the powerful anticancer properties of cisplatin, a platinum compound, the Michigan State University (MSU) physicist is still glowing. Says Rosenberg, "It continues to surprise me how good the stuff is."

Cisplatin is the best new cancer drug to come out of any laboratory in recent memory. But it is not a wonder drug, and researchers now do not really expect to find a single drug that works against all cancers. The big developments, rather, are coming out of cancer clinics where scientists blend promising discoveries like cisplatin into innovative treatments that, sometimes, do seem to work miracles.

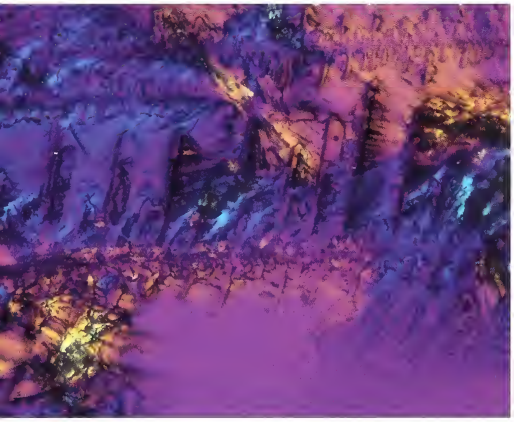
"The most important development in the past 15 years has been the use of drugs in combination," says Dr. Gregory A. Curt, former deputy director of the NCI's Division of Cancer Treatment. Two cancer drugs often fight the same tumor in different, complementary ways, he explained. When combined, they produce an "additive" effect on the tumor roughly equal to the sum of the strength of the drugs acting alone. Some drugs will boost each other to produce an even more powerful "synergistic"

Dr. Barnett Rosenberg experimented in the early 1960s with the effect of electricity on cell division. His research highlighted the potential of cisplatin as a new cancer drug.

effect. In an ideal combination, the side effects of each drug are different and neither add to nor boost those of the others.

"The second most important discovery was really a leap of faith," Curt says. "Could you ethically treat patients whose cancer had been removed surgically and who had no obvious residual tumors with these combinations of drugs in the hope that you would kill any unseen tumors...? The answer was yes."

With certain cancers, many patients relapse after the obvious tumor is removed, even though there are no further signs of disease at the time of initial treatment. Chemotherapy, however, often can wipe out unseen cancer cells that probably remain. Although it took faith in the 1970s to give this adjuvant chemotherapy to overtly cancer-free patients, clinical trials in the past five years have proved that the treatment greatly increases a patient's chance of surviving this disease.



The platinum compound cisplatin, a single crystal of which is shown here, broke new ground in the evolution of cancer chemotherapy.

Young men seldom get cancer. But when they do, it is often testicular cancer, the most common tumor from age twenty to thirty-four. About 5,600 new cases were expected in 1988. Fifteen years ago, the disease progressed to the advanced stage in nearly half the patients, where it killed nine out of ten within a year, nineteen out of twenty within two. Today, however, testicular cancer is one of the most curable malignancies, with a survival rate better than 95 percent. The thanks goes to the power of cisplatin in combination drug treatments.

The cisplatin story begins at a MSU lab in 1961, where Rosenberg was trying to find out if electricity plays a role in cell division. In setting up the experiment, he made the fortunate mistake of using platinum electrodes, in the belief that the metal would not react with the bacteria he was growing in an ammonium chloride culture solution. Turning on a low-level current, Rosenberg found that he could influence the bacteria's growth. In fact, the usually short bacteria grew into filaments 300 times their normal length. Something was keeping them

from dividing into new cells. It took four years to identify that "something" as cisplatin, formed by the action of electricity on platinum that had dissolved into the culture solution.

If cisplatin could keep bacteria cells from dividing, Rosenberg thought, perhaps it could prevent cancer cells from dividing and thereby block their growth. In 1968 he tested the compound on mouse tumors: "We knew then that it had anticancer activity," Rosenberg says today.

Rosenberg brought cisplatin to the NCI once he knew that it worked against mouse tumors. He was met with skepticism. Platinum is a heavy metal that, until then, was thought too poisonous to use in humans. But, the NCI put the compound through its own screen and confirmed cisplatin's strong anticancer activity. Researchers quickly synthesized the drug at the Wadley Institutes of Molecular Medicine in Dallas, ran safety trials in animals with cancer, then tried it in patients. The results were announced in 1971. "We felt that it had a wide range of applications," says Dr. Joseph M. Hill, then director of the Institute. But cisplatin also produced some dangerous kidney side effects. Researchers elsewhere soon reported similar troubles, and some wondered if the drug was too poisonous to give to patients. Cisplatin presented a dilemma: "It's too good a drug to drop," Hill said, "and it's too bad a drug to continue."

Clinical testing did go on. Based on trials at the Roswell Park Memorial Institute in Buffalo, Drs. Donald J. Higby and James F. Holland reported in 1973 that cisplatin was particularly effective against testicular cancer. Then Dr. Esteban Cvitkovic developed a "pharmacologic trick" to protect the kidneys of patients getting cisplatin at the Memorial Sloan-Kettering Cancer Center in New York. Cvitkovic gave patients large amounts of water during treatment to wash the drug quickly through the kidneys before it could damage them. With this hydration, cisplatin could be given at levels more than twice the earlier safe

The development of cancer drugs has given clinicians new tools to be used as adjuvant or primary therapy.

Dr. Gregory A. Curt (right) reviews treatment and progress with a lymphoma patient who has been treated with radiation and chemotherapy.

dose. Said Rosenberg, "Cvitkovic came along just at the right moment."

The first combination to work well against testicular cancer, though, did not include cisplatin. In 1970 Dr. Melvin L. Samuels had tried the drugs vinblastine and bleomycin on patients with advanced cancers at the University of Texas M. D. Anderson Cancer Center in Houston, and reported a synergistic effect and a cure rate near 40 percent. When Dr. Lawrence H. Einhorn added cisplatin to these drugs at the Indiana University Hospital in Indianapolis in 1974, he got a very pleasant surprise: The PVB combination (platinum, vinblastine, bleomycin) scored 70 percent, nearly twice as good as Samuels' results, and fourteen times better than the two-year survival rate just five years before.

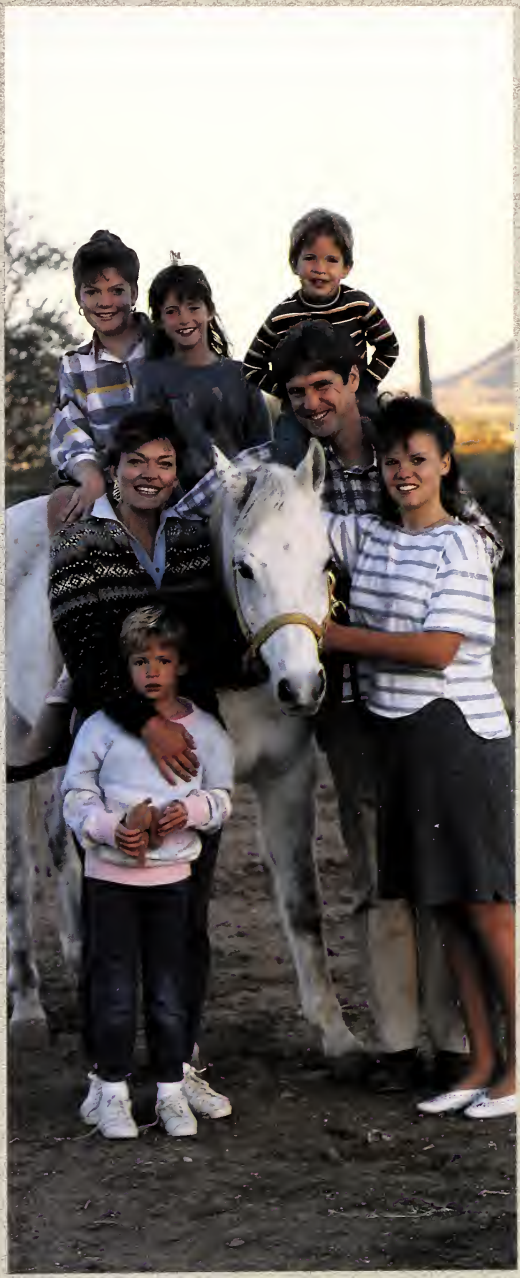
"This turned out to be, even in my optimistic thinking, much more effective than I would have dreamed," Einhorn said. "There has probably never been such a dramatic change in such a short period of time in a cancer that was rapidly, uniformly fatal."

With a cure rate of 70 percent, Einhorn could "statistically afford" to confront the side effects of the most troublesome drug in the PVB regimen—vinblastine. It destroyed white blood cells and depressed the immune system, leading to infections that hospitalized 40 percent of the patients and killed one in twenty-five. If cisplatin was the most powerful of the three drugs, could you reduce the vinblastine—and its side effects—without reducing the rate of cure? In a second clinical trial, Einhorn tested a new PVB recipe with 25 percent less vinblastine and got the same 70 percent cure rate. But it also cut the death rate from side effects in half and reduced the proportion of hospitalized patients to 15 percent.

Hoping to move even faster on this promising treatment, in 1978 the Indiana University Hospital and seventeen other institutions in the Southeastern Cancer Study Group pooled their patients in a series of trials to develop better drug combinations. Over eight years the group completed studies showing that:

- the cure rate could be raised another

Dr. Lawrence H. Einhorn was the first to add cisplatin to combination chemotherapy for testicular cancer. With the new mix, survival rates soared.



Cisplatin: Treatment Success

Nearly two decades after winning three gold medals and one silver for swimming in the Olympics in Mexico City, Charlie Hickcox shows few signs of slowing down. He has built a 20-yard exercise lane in his pool and plans to build basketball and tennis courts on his grounds. And he shows few signs of the rare germ cell cancer that was discovered in his chest a few days before Christmas 1980.

After a 3½ pound tumor was removed, Hickcox was treated with combination cisplatin therapy by Dr. Lawrence H. Einhorn at Indiana University Hospital. Even before treatment was completed, Hickcox was shooting baskets, playing tennis and working as a corporate attorney. Today at forty-one, he develops real estate around Phoenix and spends time in family activities with his wife Susan and their five children.

The discharge planning team of nurses, physicians, chaplains, social workers, dietitians, pharmacists and therapists, which carefully evaluates the continuing needs of each patient and family, takes on increasing importance as patients throughout the country are leaving the hospital sooner and continuing treatments at home. "Continuity of care—that is our goal," says Annette Bisanz, clinical nurse specialist for discharge planning at the University of Texas Cancer Center. "Good patient care should not stop at the hospital door."

More and more oncology nurses, like Ellen McCarthy, are becoming Clinical Nurse Specialists by earning master's degrees that advance and hone their skills in the clinical care of cancer patients. "I love to care for and build relationships with patients," says McCarthy, who looks after patients at the Houston Cancer Hospital. "The master's degree has made me more confident about what I have to give as a nurse." Oncology nurses not only are specialists in supportive care, but also are invaluable guardians of patients' conditions. "Because nurses spend the most time with the patients," McCarthy says, "we are able to spot potential problems early and alert the doctors."

Nurse Jeanette Carusa, on the right in the photo above, teaches a patient how to use an infusion pump. "Not too long ago, all patients who were receiving intravenous chemotherapy had to go to a hospital or doctor's office," says Debbie Armstrong, director of nursing for the Ambulatory Treatment Center at the Houston Center. "Now they can administer their chemotherapy at home." The Texas nurses reflect changes in cancer nursing seen throughout the country.

Bags of chemotherapy drugs hang ready for outpatients. On a busy day, the nurses will administer these life-saving drugs to more than 150 outpatients, who receive treatment in comfortable, private rooms surrounding the nurses' station.

Meeting the Challenge of Patient Care

Providing a personal touch is an integral part of caring for the cancer patient, as attested by these oncology nurses at the University of Texas M. D. Anderson Cancer Center in Houston. At the same time, these specialists have responsibilities beyond traditional nursing duties. All undergo intensive training in every aspect of cancer care. They work closely with physicians as part of the medical research team. They administer powerful anticancer drugs and participate in hundreds of clinical research protocols.

Oncology nurses also are the keystone of patient education. They are the source that patients and families most often turn to when they have questions about cancer. The nurses are asked to teach patients sophisticated information about the disease; they lead classes on chemotherapy, nutrition, and catheter care. And they advise families on supportive care away from the hospital.

Drug Resistance

One of the obstacles to successful cancer treatment is drug resistance. In some patients drugs kill cancer cells, while in others, drugs have no effect.

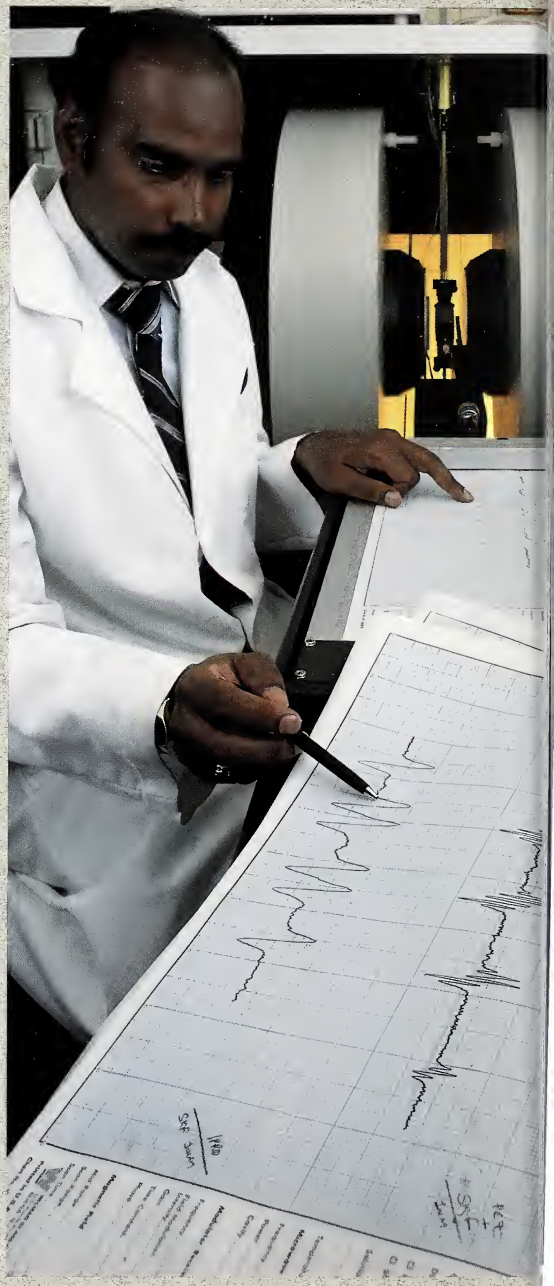
Recently, scientists have found new clues to why cancer cells resist drugs. These include a protein that pumps drugs out of the cell, and enzymes that neutralize drugs.

Some types of cancer, including colon, liver and kidney, resist drugs from the outset. Scientists have discovered that normal cells in these organs fend off environmental toxins by using a protein that traps them and rapidly flushes them out of the cell. If such cells become cancerous, they treat anticancer drugs just as they would environmental toxins, and pump them out.

Other cancers are initially responsive, but if cancer returns, the cells show resistance. In such cases, the drugs may have killed most of the cancer cells but left a few resistant cells unscathed. As these cells multiply, the cancer recurs.

In the search for ways to disarm or circumvent drug resistance, researchers are turning to the science of genetics. For example, scientists have been able to isolate the gene for the protein pump. By transferring this gene into drug-sensitive cells, they can convert them to drug-resistant cells. Alternatively, transferring this gene into normal bone marrow may shield developing blood cells against the impact of chemotherapy.

Numerous agents that reverse drug resistance in the laboratory have been identified, and some are currently in clinical trials.



Dr. Birandra K. Sinha uses electron spin resonance spectroscopy to examine the role of free radicals in promoting anticancer drug activity as well as in the development of drug resistance.

10 percent by using cisplatin and a new drug, etoposide, as second-line therapy for patients not cured by the PVB regimen.

- 20 percent of those who failed this second-line therapy could be cured by cisplatin and another new drug, ifosfamide.
- the two-year "maintenance" regimen of vinblastine, which normally followed the 12-week PVB treatment, was unnecessary.
- vinblastine could be dropped altogether from the PVB regimen and replaced by less-toxic etoposide.

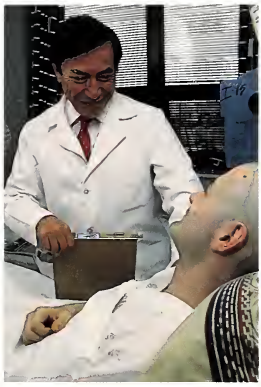
"We now have the wherewithal to pretty well guarantee that virtually every single patient with stage I and stage II disease will be cured," Einhorn says. "Eighty percent of the patients with stage III disease will be cured with first-line or second-line chemotherapy, and probably closer to 85 percent now with third-line therapy. And that's pretty impressive."

Adjuvant chemotherapy—the leap of faith in cancer treatment—has been equally impressive against osteosarcoma, a bone cancer that each year strikes more than 900 people. Most of them are adolescents. Fifteen years ago, the only treatment was to amputate the cancerous arm or leg. Even then, barely 20 percent of the patients survived. Adjuvant chemotherapy has changed that. Today, the cure rate stands between 60 and 80 percent, and half the patients survive without amputation.

Prior to 1972 this cancer had withstood every kind of cancer drug. "Chemotherapy for osteosarcoma," one doctor said then, "is like pouring boiling water on a billiard ball. It doesn't melt."

During the 1960s, Dr. Isaac Djerassi at the Children's Hospital of Philadelphia developed a technique with non-Hodgkin's lymphoma patients that eventually would affect osteosarcomas. Djerassi thought the tumor cells would die if exposed to a drug in large enough quantities. He also knew cancer cells grow faster than normal cells and absorb drugs more quickly.

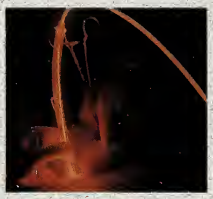
Djerassi gave non-Hodgkin's lymphoma patients extremely high doses of the drug metho-

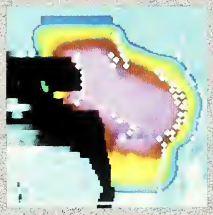


Dr. Isaac Djerassi devised a way to deliver high doses of methotrexate by "rescuing" normal cells before they could succumb to the anticancer drug.

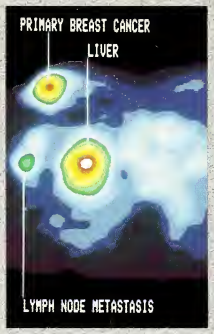
Radiolabeled monoclonal antibodies confirm that this patient's cutaneous T-cell lymph cancer involves the lymph nodes and skin. The antibodies collect in the cancerous lymph nodes of the armpits, neck and groin and a strong outline of the patient's body verifies skin involvement. The liver and spleen are darkened, too, because it is normal for these organs to collect the antibodies.

Photodynamic therapy is being studied as a treatment for selected tumors of the lung. A chemical, called hematoporphyrin, makes the tumor cells sensitive to a laser light, which is directed at the tumor cells to kill them.

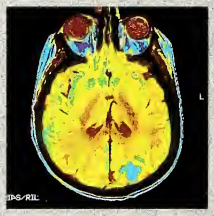




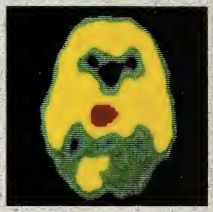
Proton beam therapy delivers radiation to a tumor at the base of the skull, while this computer-generated image displays the dosage, from the maximum (pink) down to the lowest dose (gray). The positively charged atomic particles (protons) are carefully focused to minimize harm to surrounding tissue.

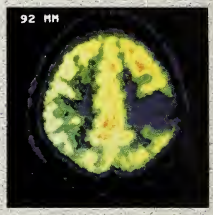


Positron Emission Tomography shows, in cross-section, breast cancer in a woman who has received an injection of low-level radioactive substance. The PET scan reveals that the cancer has spread to a lymph node. The liver, which removes the substance from the body as a normal function, also displays radioactivity.



Magnetic resonance imaging reveals a bright blue brain metastasis in the occipital lobe (lower right of image). MRI, using a powerful magnet and radiowaves, shows the difference between normal and abnormal tissue with high resolution, often picking up more subtle variations than CT scans or other imaging techniques.





In these PET scans, the top figure depicts a highly malignant brain tumor. It appears red because the tumor uses more glucose than the normal brain. The tumor in the lower figure is blue, indicating that it is not metabolizing excess glucose and is, therefore, benign. By using scans, doctors can tell if a tumor is malignant without resorting to a surgical biopsy.

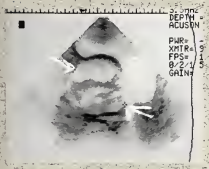
New Insights into Cancer Diagnosis and Treatment

Fifteen years ago, scientists who wanted to visualize internal body structures were limited to direct film exposure by an X-ray beam. Today, with advances in computer technology and data collection, diagnostic imaging has changed dramatically. No longer limited to detection and diagnosis, imaging offers benefits in determining stage of disease, as well as in the planning, verification and followup of treatment. In some cases sound and light waves are themselves the therapeutic weapon.

Brain and whole body imaging has revolutionized diagnosis. Computed Tomography (CT) was the first to produce pictures of organs and soft tissues comparable to those seen with anatomical dissections. Aided by computers, multiple CT scans can now be combined to produce three-dimensional images of the body. Positron Emission Tomography (PET) is an extraordinary new tool that employs tracer doses of radioactive agents to reveal cellular metabolism in both normal and malignant tissues. Magnetic Resonance Imaging (MRI) delineates anatomical and pathological changes with spectacular clarity from any angle or plane desired. The technology of ultrasound has continued to improve as an instrument for detecting tumors in the breast and pelvic region. Finally, the use of radiolabeled monoclonal antibodies promises to improve the detection of small cancers that might otherwise go unnoticed.

In treatment, proton beam therapy has been shown to effect long-term control in certain hard-to-reach head and neck cancers. Another technique called photodynamic therapy uses light beams to destroy tumor cells that have been made light-sensitive by treating them with a photosensitizer. This approach has been successful in treating certain lung tumors, superficial bladder cancer, and recurrent cancer in the skin. For localized tumors, an experimental heat treatment known as hyperthermia is emerging as a potential means of enhancing radiation therapy and chemotherapy. Heat produced by microwaves, radiowaves or ultrasound kills tumor cells without harming surrounding tissue.

This ultrasound scan shows an ovarian tumor as a large round mass (arrows) pressing against the bladder (B). Since ultrasound does not deliver potentially damaging ionizing radiation, it can be used as often as necessary to obtain detailed images of the pelvic area.



Hyperthermia also uses ultrasound to deliver heat to deep tumors. This three-dimensional image shows where the heating device (yellow knobs) sends the ultrasound waves through the skin (yellow mesh) into the tumor (blue) lying next to the bladder (purple).

Computed tomography (CT) generates a three-dimensional picture of head and neck cancers by combining information from dozens of CT scans. It shows the tumor in red; brain, brain stem and spinal column in yellow; and lung in green. This diagnostic method helps doctors plan the radiation treatment by pinpointing the critical structures (yellow and green) that must be avoided when irradiating the tumor.

trexate, but just long enough for the cancer cells to drink a fatal dose. Then he "rescued" the patients with an antidote that neutralized the drug before it could kill normal cells. At the Mercy Catholic Medical Center in Philadelphia, Djerassi gave up to 1,000 times the normal dose of methotrexate and still rescued his patients unharmed.

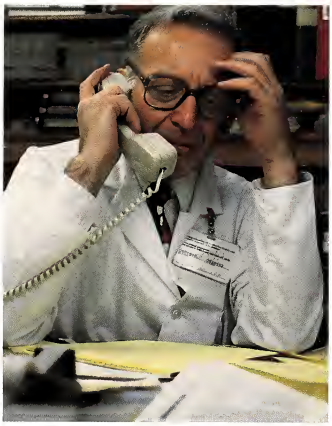
Combined with other drugs, this high-dose methotrexate helped cure six of twelve children treated in 1967 and 1968.

Djerassi's daring work was considered "crazy" by some, but it aroused the interest of researchers at the Children's Cancer Research Center in Boston (now the Dana-Farber Cancer Institute). There, in 1971, Dr. Norman Jaffe, collaborating with Djerassi, began giving high-dose methotrexate to patients with advanced osteosarcoma.

After raising the treatment to 400 times the standard dose, Jaffe finally saw tumors in four of his ten patients stop growing. Some even began to shrink.

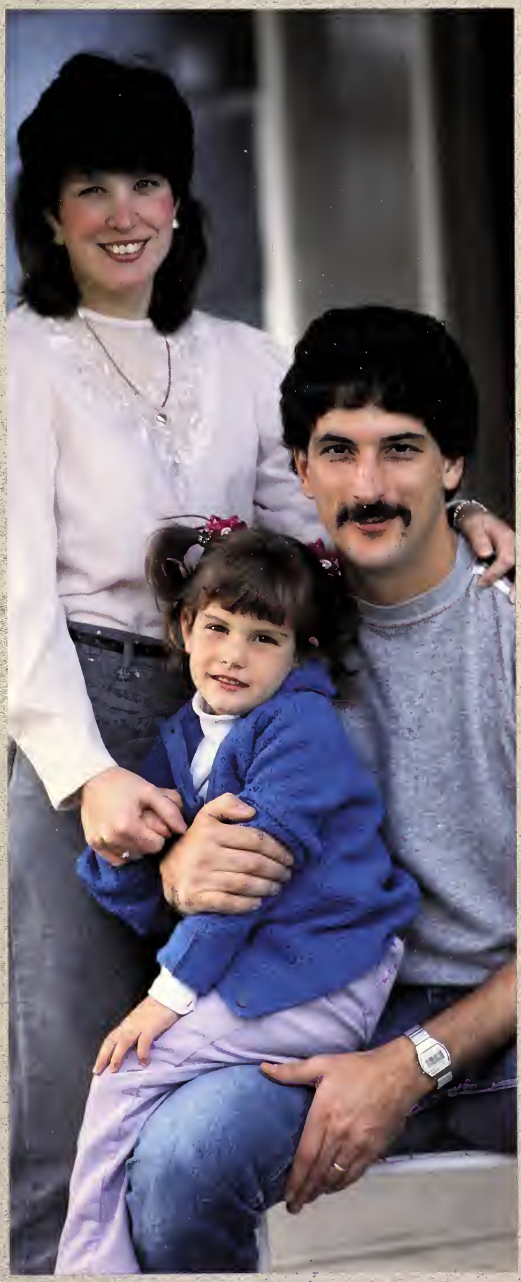
If high-dose methotrexate could reduce large, visible tumors, might it be powerful enough to wipe out unseen, microscopic tumors as well? It seemed likely that most osteosarcoma patients had such microscopic tumors. Before 1972, 80 percent of these people relapsed and died even though they showed no other signs of disease when their cancerous limb was removed. Jaffe took the leap of faith and began giving adjuvant chemotherapy: high-dose methotrexate immediately after amputation. The results in 1974 showed a survival rate above 40 percent, more than twice the historic figure of 20 percent.

Drs. James F. Holland and Engracio P. Cortes reported similar results the same year with doxorubicin (Adriamycin) as adjuvant chemotherapy for osteosarcoma patients treated in multi-institutional studies of the Cancer and Leukemia Group B Study Group. Since doxorubicin and high-dose methotrexate each cured another 20 percent of the patients in addition to the 20 percent cured by amputation alone, researchers speculated that the two drugs plus



Dr. James F. Holland led multi-institutional studies in the 1970s which demonstrated that high doses of a pair of anticancer drugs tripled the survival rate for osteosarcoma patients treated by amputation.

Dr. Ralph C. Marcove, shown here holding a metal, limb-sparing replacement for cancerous bones, helped pioneer the use of adjuvant chemotherapy in osteosarcoma patients.



New Treatment for Bone Cancer

For many years, a diagnosis of bone cancer meant amputation of the diseased arm or leg. But in 1974, a Long Island teenager named Amy Giardina became the first osteogenic sarcoma patient to have her diseased hip, thigh and knee replaced with a metal implant. Because it took so long to fashion the prosthesis, Drs. Ralph C. Marcove and Gerald Rosen at Memorial Sloan-Kettering Cancer Center decided to start chemotherapy before her operation. That decision helped revolutionize bone cancer therapy; with preoperative therapy survival rates have improved dramatically.

Today, Giardina is a homemaker who last year gave birth to her second child. Giardina's knee is stiff, but that doesn't stop her from hoisting the baby on one hip and going about her daily chores, which include gardening, needlepoint and caring for her school-age daughter.

Oncologist Dr. Greg McCormack heads the Fargo, North Dakota CCOP, at St. Lukes Hospital-Merit Care one of 52 such programs in thirty-one states.

"Many cancer patients in rural North Dakota and Minnesota can't travel to a large cancer center," McCormack says. "We provide them with first-rate care near their homes."

amputation might have an additive effect of 60 percent. In 1974 the Boston team started giving full doses of doxorubicin and high-dose methotrexate after surgery. The regimen ultimately produced a 59-percent survival rate, almost exactly the figure predicted.

At Sloan-Kettering in New York, Dr. Ralph C. Marcove was developing a procedure to save limbs from amputation by replacing the cancerous bone fragment with a metal prosthesis. To stabilize the cancer while the prosthesis was made, Dr. Gerald Rosen in 1973 started giving combinations of high-dose methotrexate and other drugs to Marcove's patients before surgery as well as after. The doctors found that the preoperative drug treatment often shrank the tumor, made limb-salvage surgery easier, and helped fight microscopic disease. In fact, they eventually achieved a cure rate exceeding 70 percent. For patients who did not respond well to preoperative treatment, in 1978 Rosen began adding cisplatin and doxorubicin to their postoperative combination. This adjuvant treatment helped push the overall five-year cure rate to more than 80 percent.

The figures are impressive. But not everyone in the cancer research community during the mid 1970s believed that high-dose methotrexate was responsible for the increased cure rates being reported for osteosarcoma. These improvements were based on comparisons with the historic cure rate of 20 percent with amputation only. Some researchers, however, suggested that natural changes in the disease plus new technology enabling earlier and more accurate diagnosis had raised the five-year survival rate to over 40 percent—without the help of chemotherapy.

"I don't believe, in 1974 when the first studies came out, that there was any proof that high-dose methotrexate as adjuvant chemotherapy worked," said Dr. John H. Edmonson of the Mayo Clinic in Rochester, Minnesota. "Until someone proved that something was better than nothing, there was a need for controlled studies."

CCOP: A Cooperative Venture In Treatment Research

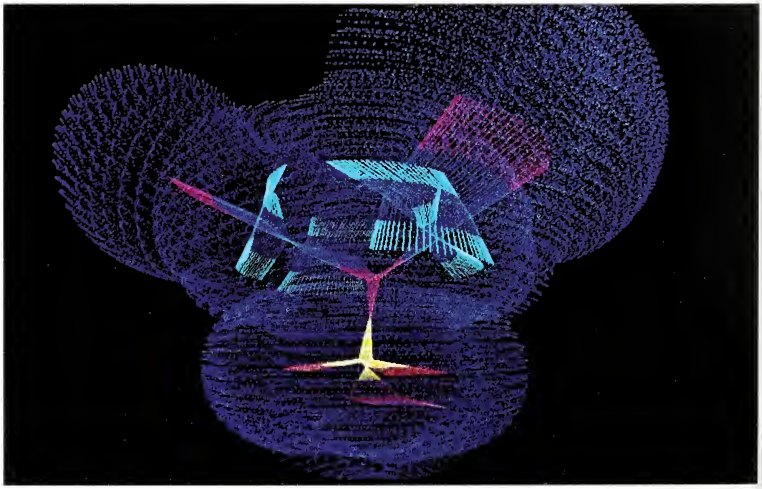
The NCI's Community Clinical Oncology Program (CCOP) brings the latest cancer treatment research into local communities, where 80 percent of cancer patients receive their treatment. It works through community physicians and hospitals that affiliate with major NCI-supported research centers to participate in large clinical trials.

Launched in 1983, the CCOP entered more than 13,000 patients in research studies in the first three years. Much of the improvement in survival data over the past decade can be traced to widespread participation in clinical research protocols, and this program is expected to strengthen that trend. "Many lives have benefited," Fargo's Dr. Greg McCormack affirms. Moreover, by increasing the number of patients in treatment studies, the program is reducing the time needed to answer important questions about new therapies.

To answer this question, the Mayo Clinic began a controlled study of osteosarcoma patients in 1976. This study was closed early, with only thirty-eight patients, when researchers observed that the group that received high-dose methotrexate after surgery and the group that did not receive the drug survived equally well. In fact, over 40 percent of both groups survived five years. "Because of the small number of patients and changes in the standard regimens," Edmonson says, "the study failed to resolve the issue."

"This controversy made it impossible for anyone to believe chemotherapy was working," said Dr. Michael P. Link of the Children's Hospital at Stanford in Palo Alto. "Nobody knew what the state of the art was." Link and others advocated new controlled studies to settle the question.

Jaffe, the first to try high-dose methotrexate on osteosarcoma, argued against additional controlled studies. It is unethical, he said, to put patients into a control group without chemotherapy if you know that chemotherapy does work. And, he added, the results of recent trials, compared to the historic cure rate, were



Super computer modeling to determine the structure of anticancer drugs and their breakdown products, such as phosphoramide mustard shown here, helps scientists understand how the drugs behave at the level of atoms and molecules.

sufficient proof that adjuvant chemotherapy does work. Holland concurred.

Dr. Emil Frei III, director of the Dana-Farber Cancer Institute, agreed that this adjuvant chemotherapy was effective against osteosarcoma, but he backed the call for controlled studies. "I know a lot of patients were being suboptimally treated because doctors just didn't believe it," Frei said. "If the doctors out there don't believe you...they don't do what they're supposed to do with their patients. So your accomplishment is not meaningful." Two multi-institutional controlled studies were set up, one in 1981 and another a year later. Both were stopped in 1984 after showing roughly the same results. "It became obvious from the first patients that the chemotherapy patients were doing much better," said Link, who headed one of the studies. "It became unethical not to treat people with chemotherapy."

The controlled clinical studies at last established a consensus that combination drug regimens were effective as adjuvant chemotherapy for osteosarcoma. But, after all, were the controlled trials necessary? "If you really don't know the answer, it's the ethical thing to do. We did not know the answer," says Curt. "The answer turned out to be yes...it really affected how physicians treat patients with osteosarcoma."

It took twenty years to turn Djerassi's "crazy" idea about high-dose methotrexate into a high-cure treatment acceptable to doctors who care for patients with osteosarcoma. It has taken nearly as long to develop a cisplatin regimen for testicular cancer. These treatments show that there is no easy, quick way to develop a cure for cancer. But they also prove that it can be done.

"It may be that somebody will come up with a fantastic development that knocks out all cancers at one time, but I don't think so," says Rosenberg. "Each one of them is going to take a lot of work and a lot of improvements and a lot of finagling with little details.... But I think a very real appraisal suggests that one by one the cancers will go down."

Cancer Survivors: Meeting Life's Challenges

Half a century ago only one in five cancer patients lived five years after diagnosis. Now, almost half survive the disease for five years or more. Today, five million Americans can call themselves cancer survivors, but they are facing challenges rarely met before. More cancer patients now receive treatment at home or as outpatients for months or years. With help from a multidisciplinary team of health care professionals, patients and their families can make a smooth transition from the hospital to home so they can lead more normal and fulfilling lives.

Part of leading a normal life means returning to work. Even though some cancer survivors have experienced job discrimination and trouble getting health and life insurance, most are able to work and build their careers. For some, cancer has made them less afraid of new experiences.

"Cancer pushed me. It's made me do more with my life," says Clarice Paloni of Albuquerque. "I'd procrastinated about remodeling an old motel. After I was sick, my first project was to rip out the motel rooms and put in offices."

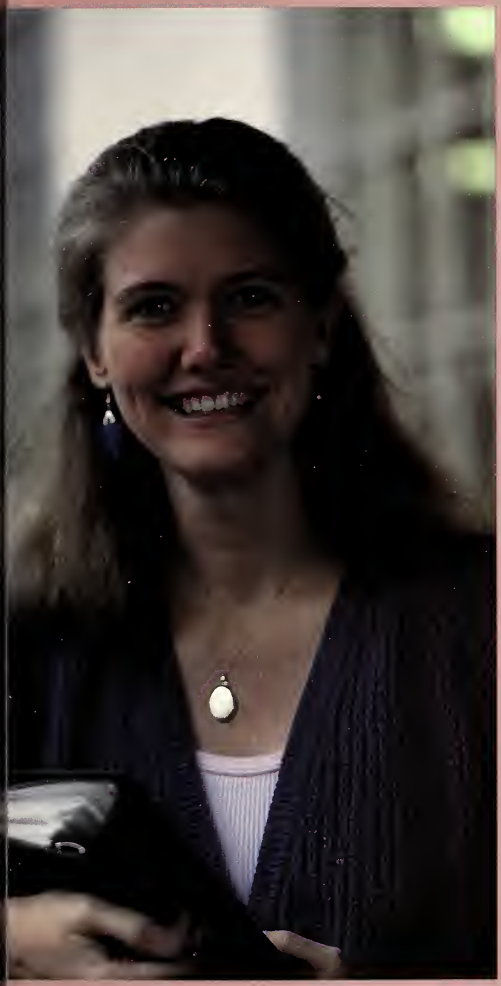
Returning to school and finishing an education often concern young cancer survivors. In an NCI study, 86 percent of 2,283 survivors went on to graduate from high school and about 50 percent finished college, percentages equal to those for the general population.

Young cancer survivors also wonder if they can someday have children. Although some cancer treatments can reduce the chances of becoming a parent, the good news is that many people who have survived cancer in childhood and adolescence are indeed having healthy children of their own. In an NCI-funded study of 2,308 children of survivors, only seven had cancer and seventy-eight had birth defects. Both of these figures are comparable to those for the general population.

Jason Prieto, a handsome, bilingual Cuban-American teenager, maintained a B average, played on his high school tennis team and played racquetball—all while he was receiving chemotherapy for Hodgkin's disease. Diagnosed at age fourteen, he was first told he would have to miss a year of school during treatment. But he received chemotherapy only on Fridays and Saturdays for nine months, and, as he says, "kept the frame of mind that I would do well." He did.

He helped start a support group for adolescents with cancer, and worked with younger patients, too. Prieto graduated with special recognition and is now studying engineering at Florida International University.

Beth Nance is popular and intelligent. But more than this, she contends, "I am one of God's miracles." While a junior at Baylor University in Waco, Texas, she was diagnosed in February 1986 with Ewing's sarcoma, a rare bone cancer. After six months of chemotherapy, followed by surgery in August to replace the diseased part of her right thighbone, Nance surprised the doctors by returning to school in September. Despite monthly visits to the University of Texas M. D. Anderson Cancer Center in Houston for chemotherapy, she attended classes, went to sorority meetings and was elected Homecoming Queen. Using a cane, she walked across the commencement stage in May 1987 to receive her diploma. She now teaches high school English and is assistant director of a girls' drill team.



Kathreen Gimbrere, twenty-nine, shows no sign of Hodgkin's disease, the lymph system cancer that developed during her senior year at Harvard University. In December 1979, surgeons removed several malignant lymph nodes from her neck. On New Year's day, her spleen was removed. She received chemotherapy for six months and radiation for several more.

She chose to remain a part-time student, graduating as a literature major just a year behind schedule, and then began working at Boston's Dana- Farber Cancer Institute where she became a cancer research assistant. She subsequently decided to make medicine her career and is now a second-year medical student at Cornell University Medical College.

Gimbrere says cancer made her a more serious person, but it also heightened her joy in living. "Mostly, I am glad to measure my present life, not in terms of what it once was or what I might have wished it to be, but in terms of how fulfilling it is now."

At twenty-five, Byron Shankles is a 6-foot, 180-pound communications technician. He plays softball, water-skis, camps, fishes and hunts.

Seven years ago, just two weeks after competing in the state semifinals with his high-school football team, Shankles learned he had testicular cancer. He was given just two weeks to live. Admitted to the NCI's Clinical Center in Bethesda, he received intensive, experimental chemotherapy for the next four months. He returned home to Alabama in April, 1981, 50 pounds thinner. But thanks to tutors at the Clinical Center, he returned to school and graduated with his class.

A year later, after regaining his strength by working on his uncle's farm, Shankles completed courses at a technical school and now works in telecommunications.

At age twenty-four, Wing Chung was found to have a rare tumor pressing against the pituitary gland in the middle of his head. Nosebleeds, headaches and double vision plagued him. He underwent two operations with radiotherapy in between, but, as expected, the tumor could not be completely removed. So his doctors tried new treatment that directs a highly focused beam of protons at the remaining cancer cells, destroying the cancer without harming surrounding tissue. A third operation to correct the compression of his eye muscles improved his vision, but he still needs to take headache medication. He also takes hormones to compensate for loss of pituitary function.

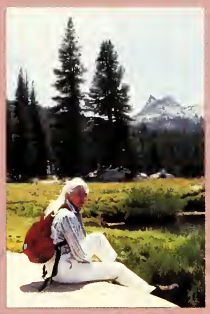
Eleven years later, Chung is clinically well. With a new job in Boston's Chinatown, he's socializing more and plans to do some traveling. "My illness set me back a little," Chung says, "but I'm finally starting to kick up my heels."

Jay Weinberg has the quiet smile of a man with a purpose. A three-time cancer survivor, this businessman now helps other cancer patients. With partner Priscilla Blum, an eighteen-year survivor of breast cancer, he founded the Corporate Angel Network (CAN). Some 400 CAN businesses donate empty seats on their corporate jets to fly cancer patients to and from treatment centers.

In 1974, a malignant mole was removed from Weinberg's back. Four months later the cancer was found in his lung. After one lobe was removed, he took the experimental drug *C. parvum* for four years to boost his immune system. During treatment, Weinberg helped start a program for recovered cancer patients to share experiences with newly diagnosed patients. Three years ago, Weinberg developed colon cancer and surgeons removed part of his large intestine. Today, he shows no signs of cancer and refuses to slow down. His wife complains that he works harder now than ever, and he replies, "I have more to work for."

With the extent of Nansea Chandler's disease—melanoma that had spread through her skin, liver, and lungs—she would not have lived for many more months. But she opted to be the first patient to enter a clinical trial of IL-2 (interleukin-2) and cyclophosphamide (an anticancer drug) as an outpatient at the University of Southern California's Comprehensive Cancer Center in Los Angeles. As successive patients entered the program, Nansea became their unofficial "greeter," explaining some of the side effects she had experienced and providing positive reinforcement. Her own cancer disappeared in six months and she remained cancer free for one year, off all treatment for over half of that time.

Once treatment stopped, she was intent on living life to



its fullest. Her activities included hikes in the Sierra, snow skiing, racquetball and tennis. And she got married.

In December 1987, cancer recurred at a new site—her brain and spinal cord. She died in April 1988.

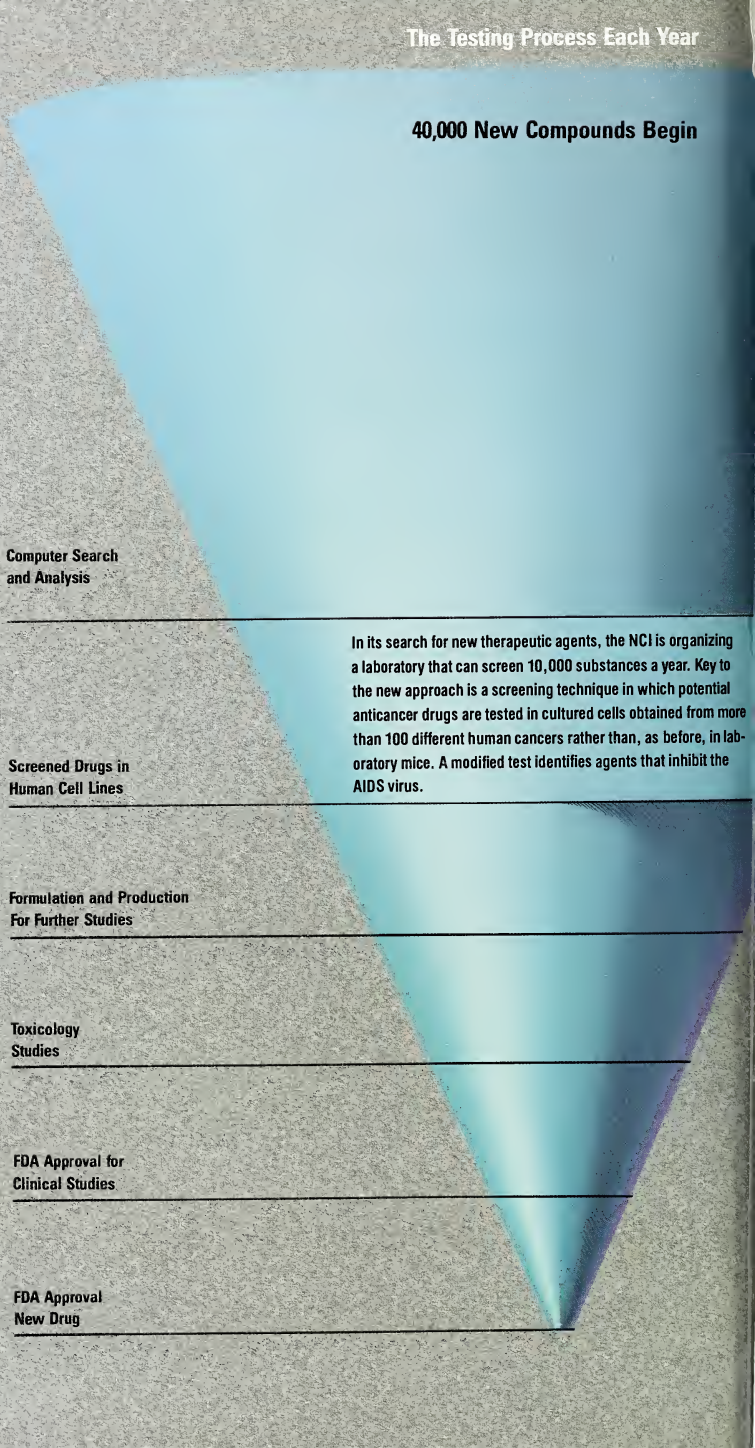
"Nansea withstood intensive treatments with an incredibly positive attitude," said her physician, Dr. Malcolm S. Mitchell. "She was a true heroine and an inspiration to everyone who knew her."

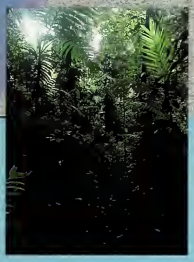
Bettye Battle spent twelve years as a breast cancer survivor after a radical mastectomy when she was thirty-nine. Then, a new cancer appeared in her right breast and spread to two lymph nodes. Because of treatment advances since her first operation, she had a modified mastectomy and chemotherapy. As of August 1988, Battle has spent three years free of disease.

"God blessed me and I came through," she says. She refused to let her family overprotect her and, instead, has spent her time helping others. Since 1975 she has worked as a volunteer in the American Cancer Society's Reach to Recovery program.

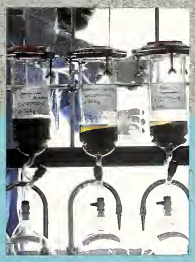
Developing New Cancer Drugs

Drug development is a complex, exacting, and time-consuming process. Of some forty thousand compounds that arrive at the NCI each year from the world's labs and markets, approximately ten thousand pass NCI computer checks designed to make sure they have a unique structure as well as some likelihood of showing some activity against cancer or AIDS. The NCI's new screening program, which uses cell lines derived from human cancers, narrows the ten thousand to about ten. These candidates then begin several years of preclinical development, and must win approval from the Food and Drug Administration (FDA) before entering clinical trials. Cancer researchers hope that the new screen, coupled with revisions of FDA regulations that set safety and effectiveness requirements for tests in patients, will streamline current development efforts.





The NCI has taken its search for new drugs to the rainforests of South America and Africa and the seas off Australia, where botanists and marine biologists collect samples of rare plants and deep sea life. Natural materials often yield potent drugs; for instance, powerful anticancer drugs have been obtained from the periwinkle plant and the May apple. [rainforest]



Crude materials from forest and ocean arrive at the NCI Frederick Cancer Research Facility, where an extraction laboratory prepares samples of the natural substances for chemical analysis.

Test chemicals from all sources are prepared in a series of dilutions, and the assay procedures are carried out by a highly skilled technical staff. Eventually, robots will be used to perform some of the more routine, highly repetitious chores.

In an assay developed with the help of NCI-supported scientists, color changes in the wells show what proportion of cultured cancer cells remain alive after they have been exposed to the test drug. The plates are read by computer, and results are automatically sent to a centralized computer where they are converted into graphic reports.

Animal studies are necessary to confirm *in vitro* results before trials in human beings can be considered. One new approach is to enclose human cancer cells in microscopic capsules and grow them in laboratory-bred mice, which are then treated with the test drug.

Biologicals: Using The Body's Own Methods To Fight Cancer

For thousands of years, natural substances—typically herbs or plant extracts—have been used as medicines for a wide variety of ailments. Today, a new class of weapons against cancer and other diseases is being fashioned from substances produced by the human body.

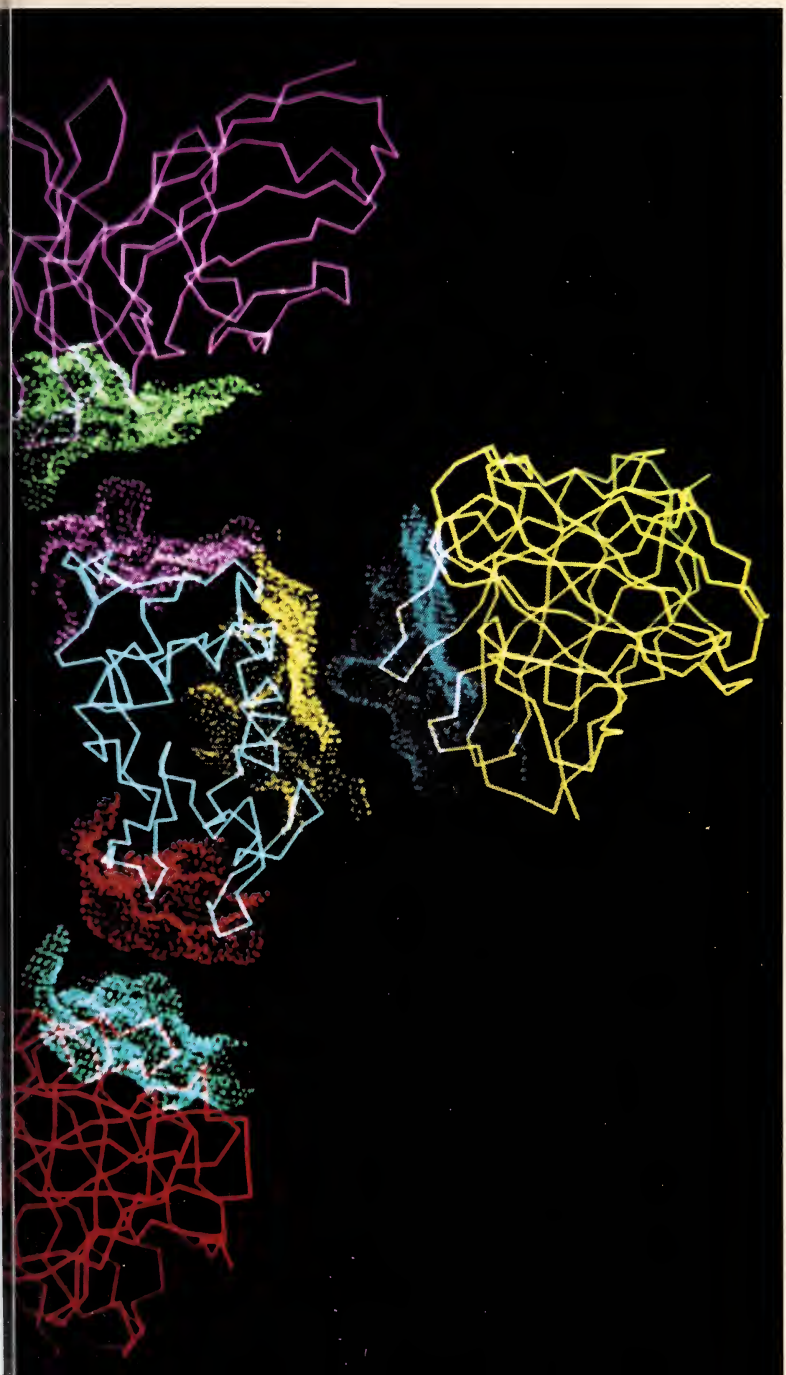
Known as biological response modifiers, these substances consist primarily of cells and cellular secretions of the body's immune and growth regulatory systems, and they fight off disease by mobilizing the patient's own immune defenses. They are often combined with one another or with other drugs.

"Biological therapy promises to make the next generation of cancer treatments safer and more effective," says Dr. Dan L. Longo, director of the NCI's Biological Response Modifiers Program.

Some biologicals have been known for many decades, but their potential for cancer therapy was limited by the difficulty of obtaining amounts large enough for clinical trials. Advances in biotechnology have changed all that, and biologicals are quickly moving into cancer treatment research.

Fully exploiting biologicals to combat cancer, most scientists agree, will demand a better understanding of the immune system as well as more information about normal cell growth. But even today they are anticipating the improvements that biologicals will bring to cancer medicine.

"There is a real excitement right now—the excitement of new doors opening, of new approaches and new strategies," says Dr. I. Bernard Weinstein, director of the Columbia University Comprehensive Cancer Center in New York City.



This computer model of three monoclonal antibodies specific for different parts of the same protein; the surface areas on both the protein and each antibody are shown by the dotted surfaces. The computer model is based on x-ray crystallographic strudtures of complexes of chicken lysozyme with the portion of the mouse monoclonal antibodies HyHEL-5, HyHEL-10, and D1.3 that contains the recognition site for the lysozyme.

Three types of biologicals may be candidates for cancer treatment: those that boost the patient's own abilities to fight disease, those that can directly attack cancer cells within the body, and natural counteragents that can subvert the ability of the cancer cells to grow and spread.

The first biologicals tested were the interferons—large protein molecules that help activate the body's immune system and also interfere with growth of viruses. Three major families of interferons—alpha, beta, and gamma, each secreted by a different cell type—are being examined as cancer treatments.

Large amounts of alpha interferon became available through recombinant DNA techniques in 1981, and thousands of patients have since received it for a broad range of cancers. Responses have been particularly promising for cancers of the blood cells—leukemias and lymphomas. Its remarkable effects in the rare form of cancer known as hairy cell leukemia—90 percent of the patients showed marked improvement—led to its approval, in 1986, by the Food and Drug Administration. Alpha interferon thus gained the distinction of becoming the first biological to be named a standard therapy for a cancer.

Studies of interferon are still under way on other forms of cancer, including chronic myelogenous leukemia and kidney cancer. These studies are attempting to establish effective dosage schedules, routes of administration, and ways to combine it with other types of treatment.

Interferon, however, is only one of many categories of molecules that can mobilize and regulate the immune system. One broad class of biologicals is known as lymphokines. Lymphokines are molecules secreted by lymphocytes, key cells of the immune system. (One form of interferon, gamma or immune interferon, is a lymphokine.)

Interleukin-2, or IL-2, discovered by NCI scientist Dr. Robert C. Gallo in 1976, is a lymphokine. IL-2, which promotes rapid growth of the white blood cells known as T lympho-

cytes and B lymphocytes, has been available in large amounts through recombinant DNA technology since 1984.

NCI's Dr. Steven A. Rosenberg and his coworkers were the first to use IL-2 to treat cancer. Rosenberg incubated white blood cells of certain cancer patients with IL-2, generating LAK or lymphokine-activated killer cells. He then returned these tumor-attacking cells to the patient, who also received additional doses of IL-2. Patients with a variety of advanced cancers, especially kidney cancer and melanoma skin cancer, showed encouraging responses.

These initial results provided the impetus for studies with large numbers of patients with various cancers, in different treatment protocols. The best way to administer LAK cells, how much to use, and how to maximize its benefits and minimize its toxicity are some of the questions being addressed.

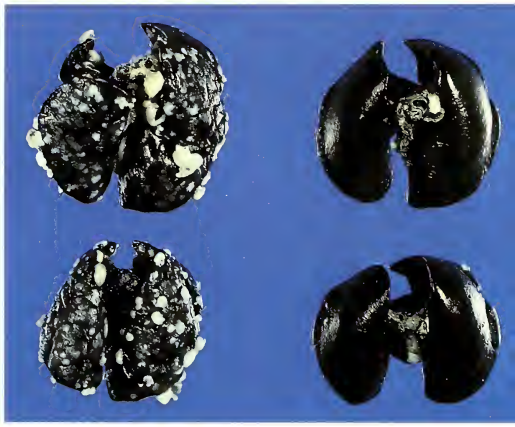
Growth factors, substances that encourage cells to grow, are another type of biologicals. One group, the colony stimulating factors or CSFs, has been known since the 1960s.

There are several types of CSF, all of which appear to help regulate the production of disease-fighting white blood cells such as granulocytes and macrophages in the bone marrow. A number of scientists are now testing these factors in patients with a variety of diseases, including cancer.

By giving marrow growth factors to patients receiving chemotherapy, which often suppresses the bone marrow's production of needed cells, scientists hope to offset some of the chemotherapy's toxicity. This would allow oncologists to launch a tougher attack on the cancer while decreasing treatment risks for the patient.

At the Memorial Sloan-Kettering Cancer Center in New York, Dr. Malcolm Moore and his coworkers have found that patients receiving granulocyte colony stimulating factor, or G-CSF, have much higher white blood cell counts than patients not receiving the biological.

Many biologicals appear to influence cells by recognizing and attaching to a specific recep-



This photo shows how IL-2 therapy has reduced the cancer in the lungs of a mouse. Animal studies have helped to demonstrate how biologicals work.

tor on the cell surface. Some cancer cells seem to be adept at producing factors supporting their own growth; others make great numbers of receptors on their surfaces that can trap large amounts of growth factor and thus "super" stimulate themselves.

At the Massachusetts General Hospital in Boston, Dr. Patricia Donohoe and her coworkers are studying a substance called mullerian inhibiting substance, or MIS. Early in the development of a male fetus, MIS attaches to receptors on the surface of the mullerian ducts, embryonic tissue that forms the uterus, fallopian tubes, and vagina. After binding to its receptor, MIS causes the mullerian ducts to shrivel, permitting the male fetal sex organs to develop.

The Massachusetts scientists discovered that, in laboratory studies, MIS also inhibits the growth of ovarian cancer cells. These cells have receptors on their surfaces that recognize MIS. A pharmaceutical firm is now developing a recombinant form of MIS so that clinical testing can begin.

Another category of biological entering clinical medicine is the monoclonal antibody. Monoclonal antibodies are the result of a technique developed in the mid-1970s by Dr. Cesar Milstein of the Medical Research Council Centre in Cambridge, England, and Dr. Georges Kohler of the Basel Institute for Immunology in Switzerland. In a collaboration that was to win them the Nobel Prize, Milstein and Kohler fused antibody-producing B lymphocytes with special laboratory-developed cancerous B cells first grown at the NCI by Dr. Michael Potter.

The fused hybrid cell, or "hybridoma," secretes the specific antibody produced by its normal B-cell parent, and continues to grow indefinitely like its long-lived malignant parent. When the hybridoma is cloned, it produces many identical offspring, each of which secretes the identical antibody. This is called a "monoclonal" antibody.

Monoclonal antibodies are now widely used in both diagnosis and treatment. Because

Dr. Steven A. Rosenberg launched a new approach to cancer therapy by taking patients' white blood cells and transforming them, in the laboratory, into tumor-fighting cells. These cells have been especially effective against advanced kidney cancer and melanoma, a cancer of the skin.

Breast Cancer: Treatment Has Changed Dramatically Since 1970

The development of less drastic surgery and adjuvant therapies has totally changed state-of-the-art treatment for breast cancer. "There's been a revolution taking place since 1970, a total revolution," said Dr. Bernard Fisher, chairman of the NCI-supported National Surgical Adjuvant Breast and Bowel Project (NSABP). Gone almost entirely is the traumatizing Halsted radical mastectomy that removed breast, underlying muscle and nearby lymph nodes which was standard treatment in the United States from the 1890s to the 1960s. In 1988, less than one percent of breast cancer surgery will be done that way.

The Halsted technique was based on the hypothesis that breast cancer is a single disease that progresses in an orderly fashion. But in the 1950s and 1960s, researchers found that it spreads so erratically that it must be considered, from the outset, to be a systemic disease in almost 80 percent of patients. Scientists now treat breast cancer as, in effect, two complex, interrelated diseases: one local-regional and the other systemic.

In a trial reported in 1977, the NSABP showed that removing only the breast (total mastectomy) plus radiating the affected area was as effective in controlling local-regional breast cancer as the Halsted technique. Then, a trial reported in 1985 demonstrated that removing just the tumor and a safety margin of surrounding tissue (segmental mastectomy, or lumpectomy), followed by radiation, was as effective as total mastectomy. Other studies showed that a boost of radiation at the tumor site—by external radiation or by an iridium seed implant—increases the therapeutic effect. This combination of limited surgery, irradiation and sometimes a radiation boost is now one of the standard treatments for local-regional breast cancer.

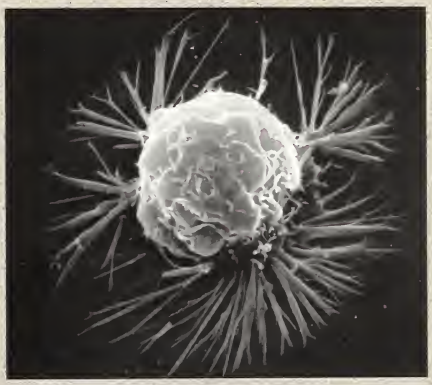
Adjuvant therapy—systemic treatment for undetected tumor cells remaining after surgery—was tested by the NSABP as early as 1958. The first clinical trial showed that chemotherapy increased survival in premenopausal women by 20 percent. Trials in the 1970s confirmed the effectiveness of adjuvant chemotherapy as well as adjuvant hormonal therapy. The anti-estrogen drug, tamoxifen, was found to increase survival by 20 percent among postmenopausal women with tumors needing estrogen for growth. Adjuvant therapy, depending on the patient and the variables of her disease, is now standard treatment for systemic breast cancer.

Women with local-regional breast cancer may benefit from adjuvant therapy, according to 1988 findings from studies funded by the NCI. These studies indicate that chemotherapy or tamoxifen therapy following primary treatment improves disease-free survival in women whose cancer has not spread to their lymph nodes.

New detection techniques, primarily mammography, have been shown to find breast cancer at earlier, more treatable stages. "We'll probably be seeing a decrease in mortality rates because of earlier detection," says Dr. Sandra Swain, a medical oncologist.

Such improvement in national breast cancer figures would be welcome. In 1988 the disease will strike an estimated 135,000 women and kill 42,000. While survival rates have been better among the few thousand women who participated in clinical trials, use of state-of-the-art treatment apparently has only begun to reach beyond research clinics. The nationwide mortality rate has remained relatively stable over the past decade and the survival rate has increased only slightly.

Fisher, however, says it is too early for treatments developed since 1970 to affect national statistics. "As more patients go onto these drugs, if they're given in the proper way," he predicts, "then we should see improvement in due time."



This scanning electron micrograph shows the surface structure of a cell from human breast cancer tissue.

each monoclonal recognizes and binds to a specific target, these antibodies can be used to distinguish among different types of cells or substances. Virtually all leukemias, for instance, are now classified according to their cell of origin—which greatly influences treatment choice as well as prognosis—with monoclonal antibodies.

Monoclonals tagged with radioactive substances and injected into the body help surgeons

Dr. Patricia Donohoe (left) and her coworkers, including Dr. Robert Still, shown with her here, have discovered that a biological that facilitates the development of sex organs in the male fetus may also block the growth of ovarian cancer cells.

locate a cancer or metastases, as well as to monitor the effects of treatment. They are also being used to help distinguish benign from malignant tumors.

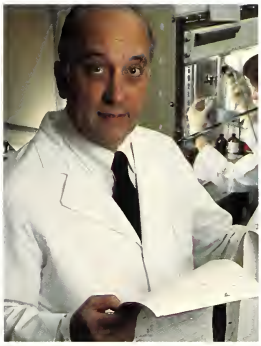
Monoclonals are also being studied as highly specific agents for delivering drugs and radioactive materials to cancer cells. One drawback to this approach is that most monoclonals now used come from mouse cells, and the immune system, recognizing them as foreign proteins, can launch an attack against them. For this reason, scientists are now working to prepare mouse-human monoclonal antibodies.

Another difficulty is that cancer cells evolve as the disease progresses, so a monoclonal that is effective at one stage of treatment may not work later.

NCI's Dr. Thomas A. Waldmann and his colleagues are one of many groups of scientists working to develop treatments that exploit new insights from both monoclonals and lymphokines. He has developed a monoclonal antibody that recognizes the specialized receptors on the surface of the T lymphocyte where IL-2 attaches to it. If this site is blocked with antibody, attachment cannot occur and the T cell cannot grow. Because certain cancer cells—those in adult T-cell leukemia, for example—constantly display high levels of the IL-2 receptor, antibody treatment leads to remission of the cancer.

The monoclonal antibody's effect lasts only a few months, however. Patients then relapse, apparently because they have developed variant cancer cells that no longer depend on the IL-2 receptor. Now, studies are trying to link the monoclonal antibody to substances such as toxins, drugs, or radioactive materials, which can kill the cancer cell once the antibody docks to its surface receptor site.

"Physicians are working with basic scientists at every stage of the development of biological treatments," says Longo. "The thrill of biological therapeutics is that what we are learning about the immune system and cancer at a molecular level is giving us new ideas for treating the cancer patient."



Dr. Thomas Waldmann and his colleagues have developed a monoclonal antibody that can block T-cell growth. It is being used experimentally to halt the growth of T-cell cancers.

PREVENTION

Although the National Cancer Program's major focus is on basic research, the application of research findings about prevention, early detection and treatment is receiving special priority.

In a 1986 report, the NCI compiled a broad range of expert perspectives into a "Goal for the Year 2000." The Goal, to cut the cancer death rate in half by the Year 2000, provides a framework for activities that can be implemented by federal and state agencies, professional organizations, private industry, and individuals.

Key objectives for the Year 2000 are:

- To reduce the percentage of adolescents and adults who smoke;
- To encourage changes in individual diets to reduce the percentage of fat intake and to increase fiber intake by eating more fruits, vegetables, beans and whole grains;
- To increase the proportion of women getting annual Pap tests and mammograms;
- To increase the use of state-of-the-art cancer treatments to improve patient survival.

Preventing Cancer: Shaping Healthier Lifestyles

By Harriet Page and Anne Rodgers

ajor benefit of the cancer research efforts of the 1970s was not only the ability to cure some cancers but a better understanding of how to approach prevention.

An hypothesis about how cells become cancerous—an initiation step followed by promotion—had been proposed in the early 1960s. Research in the 1970s and 1980s, using the new tools developed by molecular biologists, biochemists and geneticists shed new light on the steps in cancer development.

Initiation, an event that starts the process, may be an environmental insult, like exposure to a chemical, or it may be an inherited chromosomal defect. But at least one additional step, promotion, is needed to complete the conversion into a cancer cell.

Promotion events can also be environmental in origin. In the 1970s and 1980s, a host of epidemiologic studies demonstrated the role of occupational carcinogens and lifestyle factors, particularly diet and tobacco use. These studies also looked at the reasons for disparate cancer rates among subgroups of Americans. Mormons and Seventh Day Adventists, for example, have less cancer than Americans as a whole. Similarly, Asians living in the United States have less cancer, but blacks have disproportionately high cancer incidence and death rates for certain cancers.

The accumulation of research evidence that many cancers could be prevented led in the 1980s to major national efforts in applied research in cancer prevention. That research is now focused on:

- Reducing tobacco use. Americans have known about the hazards of tobacco use

National cancer prevention initiatives recommend healthier diets, less tobacco use, and good medical care.

Chewing tobacco and snuff are used widely throughout the world. "Chew or Snuff is Real Bad Stuff" is designed to alert young users to the health hazards involved.

for decades. But more than fifty million still smoke, and everyone, at one time or another, is exposed to someone else's tobacco smoke. In addition, more people, particularly young males, are picking up the smokeless tobacco habit, thereby increasing their risk of oral cancer. The NCI is now supporting more than fifty large-scale smoking prevention and cessation trials, involving over ten million people in more than 200 communities.

- Diet. Many epidemiologic and laboratory studies have shown a link between diet and the risk of developing several common cancers. Researchers are trying to learn more about the exact relationship between diet and cancer. Research is also under way to find ways to encourage people to make positive changes in their food habits. Another research program is looking at whether supplemental micronutrients, like some vitamins and minerals, can reduce the incidence of cancer. Vitamin A analogs are some of the most promising substances under study.

Tobacco

The link between cigarette smoking and lung cancer has been clear for decades. The association between cigarette smoking and cancers of the oral cavity, larynx, and esophagus also has been apparent for some time, along with evidence that it is a contributing factor for cancers of the bladder, kidney, pancreas and uterine cervix. Recent studies have clarified three other aspects of tobacco use: the harmful effects of involuntary smoking (the inhalation of smoke by nonsmokers, such as children in the home) and the cancerous effects of smokeless tobacco.

Over six million Americans now use some form of smokeless tobacco. Many users still believe, mistakenly, that the risks of smokeless tobacco are negligible and that it is much safer than cigarettes. A recent Surgeon General's Report outlined the very real health hazards of smokeless tobacco. These include oral cancer

and precancerous leukoplakias (white patches at the site where the snuff is held in the mouth), receding gums, and nicotine addiction.

Overall, trends in tobacco use have been encouraging. Since the 1964 Surgeon General's report, the percentage of adult Americans who smoke cigarettes has dropped from about 50 percent to about 30 percent. Specifically, the National Center for Health Statistics found that 52 percent of adult men and 34 percent of adult women smoked in 1966. By 1987, those percentages had dropped to 33 percent and 28 percent, respectively. A survey of 20,000 high school seniors conducted each year by the University of Michigan found that 29 percent of these young adults were smoking in 1977, but that this percentage had dropped to 19 percent by 1987. The American Cancer Society's Cancer Prevention Study II estimates that there are now about forty million ex-smokers in the United States. Says Dr. Vincent T. DeVita, Jr., former director of the National Cancer Institute, "We are seeing an epidemic of nonsmokers." This is one epidemic that he and other health officials would like to see spread, and a number of federal, state and city governments are abetting it with the enactment of "clean air" statutes that prohibit smoking in offices, restaurants, trains and other public spaces.

However, there remains a "hard core" of smokers that worries health officials. More adults than ever are heavy smokers—those smokers who have the hardest time quitting and who are at greatest cancer risk. In addition, there is also the hard core of 20 percent of high school seniors—a new group each year—who smoke. And a survey of high school dropouts estimates that 75 percent of them are smokers.

An innovative approach to this problem is the Smoke-Free Class of 2000. Responding to Surgeon General C. Everett Koop's call for a smoke-free society by the Year 2000, the American Cancer Society, the American Heart Association, and the American Lung Association have joined together in a national grassroots effort to reduce tobacco use in young people.

School-based programs, like this one in California, debunk myths and teach students ways to resist pressures to use tobacco.

Impressive evidence that dietary factors contribute to a reduced risk of cancer has stimulated a wide range of nutrition education programs for consumers.

Food labels advise consumers of fat and fiber content in frequently purchased foods. This supermarket project has started a trend toward giving consumers more nutrition information on packages.

Their efforts are focused on the three million children who will enter first grade in September 1988 and will be graduating from high school at the turn of the century. The project is aimed at parents, teachers and school personnel, and seeks to create smoke-free schools.

Meanwhile, a number of recent studies have helped to clarify why adolescents indulge in "risk-taking" behavior, and the role played by media, family and peer pressure. To reach these youngsters, a number of school-based programs have started. One program, for example, addresses the misperceptions young people have about how many of their peers actually do smoke, and also demonstrates the pressures—and how to resist them—exerted by their peers and by the advertising and entertainment industries. These school-based programs are also helping to debunk the myth that smokeless tobacco is harmless.

Another hard core of smokers are those who smoke twenty-five or more cigarettes a day, heavy smokers are being targeted in a Community Intervention Trial, called COMMIT, being conducted by ten research institutions across the country. The seven-year trial, underwritten by the NCI's Division of Cancer Prevention and Control, will test strategies to reach all smokers, but particularly heavy smokers, within selected communities.

Because smoking intensifies the effects of many workplace carcinogens, the NCI is making special efforts to reach occupational physicians and leaders of unions that include workers in high-risk jobs.

Diet

Over the past several decades, four types of epidemiologic studies have linked diet to cancer risk: international studies that compare diet and cancer incidence in various countries; "migrant" studies that show how groups of individuals increase their cancer risk as they move from their home countries to countries with higher cancer rates; comparisons of low-risk groups, like Mormons and Seventh Day Adventists, with the United States' population at large; and studies that compare dietary habits of individual cancer patients with those of the population at large.

Evidence from such studies now indicates that a diet high in fat is linked with cancers of the breast, colon, rectum and prostate, and possibly with cancers of the pancreas, uterus and ovaries. High intake of dietary fiber appears to protect against cancer of the colon. A diet rich in foods containing certain micronutrients, like vitamins C and E and carotenoid, a chemical cousin of vitamin A, is also thought to prevent some cancers.

Many studies are under way to learn more. In addition, on the basis of what is already known, both the American Cancer Society (ACS) and the NCI have launched programs to educate the public about diet and cancer. The NCI guidelines for a diet to reduce cancer risk, similar to those of other major organizations, are:

- Reduce fat intake to 30 percent or less of total calories;
- Increase dietary fiber intake to 20 to 30 grams a day, with an upper limit of 35 grams;
- Include a variety of fruits and vegetables in the diet every day;
- Avoid obesity;
- Use alcohol in moderation if at all;
- Minimize consumption of salt-cured, salt-pickled, and smoked foods.

An NCI study of the eating patterns of more than 11,000 adult Americans shows that over 40 percent did not eat a single fruit on the day they were surveyed. About 20 percent did not eat a vegetable. Also ignored by more than 80 percent of those surveyed were high-fiber cereals and whole grain breads which, along with fruits and vegetables, are potentially beneficial for preventing cancer.

"In terms of cancer prevention, women ate better than men, and people over fifty-five had better diets than younger adults," said NCI epidemiologist Blossom Patterson. "Even so, all groups showed a dramatic need for improvement. By eating more fruits, vegetables

and whole grains, Americans could increase the fiber and micronutrients in their diets, and reduce the amount of fat—possibly reducing cancer risk.''

The study, published in the March 1988 *American Journal of Public Health*, looked at data on 10,322 whites and 1,336 blacks. Blacks consumed more cruciferous vegetables and vegetables rich in vitamins A and C than whites, largely because they eat more greens, such as collards. Fruit consumption was lower among blacks than whites. High-fiber cereals and whole grain breads were more popular among whites than blacks.

As income rose, so did consumption of fruits and vegetables for both blacks and whites. High-fiber cereals and whole grain breads, often more expensive than their low-fiber counterparts, were eaten more frequently by whites but not blacks as income increased.

Many social and cultural factors influence why people eat the way they do, and health is not always a top priority. But, even when a consumer wants to follow good health guidelines, the ''how to'' is not always clear.

To see if ''how to'' information placed in a supermarket will affect food-buying behavior, and to see if the cancer prevention message is being heard, the NCI and Giant Food, Inc., a large East Coast supermarket chain, are taking part in a four-year joint study in the Washington, D.C. area, called ''Eat for Health.'' Shelf labels identify specific foods as high in fiber or low in fat. Monthly information bulletins and a guide listing the nutrient content of specific food products are available at the checkout counter. Sales data for selected foods are being tracked, and consumer studies will assess changes in attitude and behavior based on the project.

Prevention Among Minority Populations

The great gains in health care and prevention have not benefitted evenly all segments of the United States' population. A 1986 report by the ACS, *Cancer in the Economically Disadvantaged,* showed that the thirty-four million Americans who live below the poverty level have cancer survival rates 10 to 15 percent lower than the population as a whole. A 1985 report by the Secretary's Task Force on Black and Minority Health of the United States Department of Health and Human Services also showed ''distressing disparity'' in key health indicators between minority and non-minority groups, with a death rate for blacks 27 percent higher than for whites.

Both studies pinpoint a number of reasons: the distribution of health and medical resources, delays in seeking treatment, underuse of early detection measures, and home and job exposure to carcinogens. Both reports also note the greater use of tobacco and alcohol among minorities. The task force found that blacks, as a group, smoke more and develop a greater proportion of smoking-related cancers.

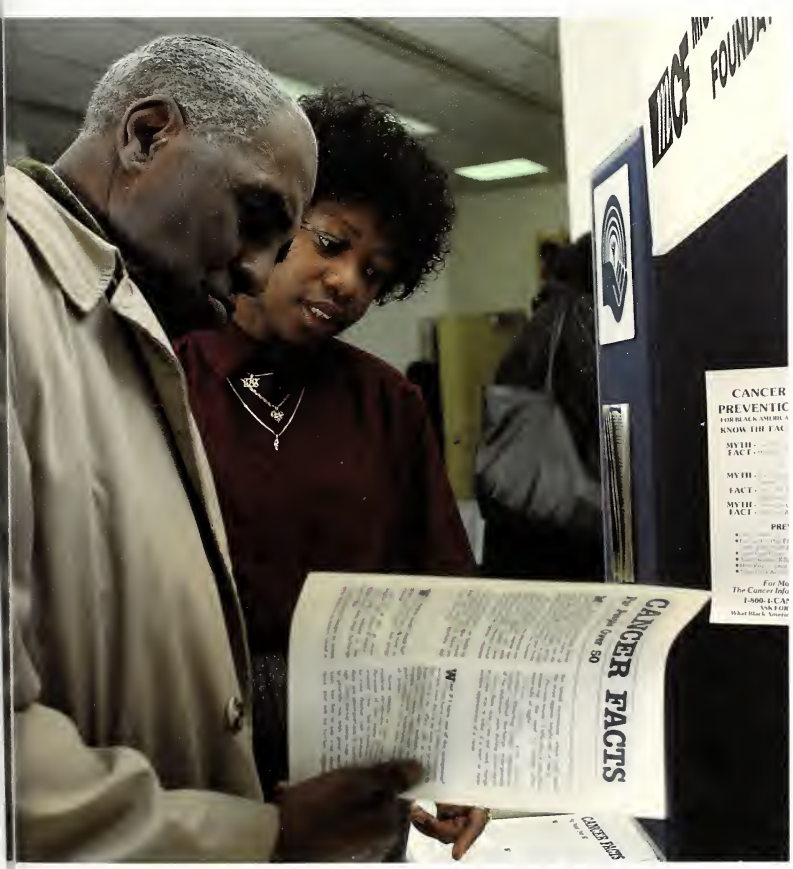
In cooperation with the Harvard University Institute for the Study of Smoking Behavior and Policy, the NCI convened a conference in March 1988 to address the adverse health consequences of tobacco use among blacks and Hispanics. Participants set priorities and recommended actions to involve community members, health practitioners and policy makers to decrease tobacco use in these populations.

In establishing a series of special minority initiatives, the NCI has given priority to: smoking cessation; early detection of cervical, breast and oral cancers; and health services access and utilization. Through its Cancer Prevention Awareness Program for Blacks, the NCI is developing information and education campaigns to motivate healthful behavior changes among all blacks. Similarly, the ACS has called for aggressive education programs for individuals and health care workers, a larger role by state and federal governments, and more culturally relevant education programs.

Over the years, the ACS has found that broadening its base of volunteers is a good way to boost awareness of specific cancer prevention measures. As one way to reach minority groups, therefore, the ACS is increasing the number of

volunteers carrying cancer prevention/public education programs aimed at early detection, smoking cessation and diet modification into minority neighborhoods and homes.

To target the specific health needs of black Americans even further, the NCI in 1985 organized a network of black investigators to help form a "critical mass" of scientists and physicians dedicated to the health needs of this population. It has also awarded planning grants to three traditionally black medical schools to develop the nation's first minority consortium cancer center. These are the Charles R. Drew Medical School in Los Angeles, the Morehouse



In Detroit, and in several other cities across the United States, coalitions of community organizations provide cancer prevention information.

Cancer Statistics: A Resource for the Nation

NCI Statistician Lynn Ries analyzes survival data and cancer patients in the SEER program, which monitors cancer rates in about 12 percent of the United States population.

Cancer accounts for about 22 percent of deaths in this country, and about 10 percent of health care costs. To monitor the impact of cancer, the NCI supports or uses a variety of statistical databases.

Cancer incidence and patient survival on about 12 percent of the country's cancer cases are monitored directly by the NCI in selected metropolitan and rural areas. A group of thirteen population-based cancer registries provides a profile of cancer among whites and minorities.

This program, the Surveillance, Epidemiology and End Results (SEER) Program, began in 1973. Now the world's largest and most consistent profile of cancer cases, SEER's computerized database contains information on over 1 million cancer cases. Annually, 100,000 more cases are added.

SEER is a resource for data on the cancer experience not only of whites and blacks, but also of Asians, Hispanics and native Americans living within its boundaries. Since 1983, SEER has also collected data on the type of surgical procedures patients received for the major cancer sites.

To aid in interpreting trends in the cancer rates, the SEER data are continuously assessed for changes in identifying, diagnosing, and staging cancer.

In addition to SEER, the NCI uses data from other sources, such as the National Center for Health Statistics (NCHS), a Federal agency that keeps records on the numbers of people who die of cancer. The NCI uses NCHS death records to examine patterns in cancer death rates in SEER registries, as well as nationwide. For example, the NCI prepared maps showing geographic shifts in cancer mortality since 1950 within the United States. NCHS also conducts an annual Health Interview Survey, containing several questions at the NCI's request on risk factors like smoking and the cost of cancer care.

School of Medicine in Atlanta and Meharry Medical College in Nashville.

Partners in Prevention, a collaboration between the NCI and community organizations or individuals active in health education has been established in a number of major cities. The first coalition, in Detroit, was organized by the Michigan Cancer Foundation and the Detroit Chapter of the National Association for the Advancement of Colored People. Capitalizing on the resources of Detroit's traditional black leadership, the program operates in the local media, schools, churches and work places. The main messages of cancer prevention have been emphasized in the media, public service announcements, bus posters, a school nutrition program for parents, a breakfast for local ministers, frequent appearances by community leaders at local functions and the annual Project Health-O-Rama screening and examination program held in 99 Detroit locations.

The growing population of Hispanic Americans is another focus for cancer control efforts. The NCI has begun a series of regional workshops to enlist the support of community agencies in cancer prevention activities. The high rate of smoking among Hispanic youth is a special concern, in addition to the need for more breast and cervical cancer screening among Hispanic women.

One example of the community-based effort that can be developed is a La Liga Contra Cancer in Miami. This non-profit clinic and outreach center offers mammograms and Pap tests regardless of ability to pay, as well as referrals to local cancer treatment facilities. La Liga and the NCI's Cancer Information Service refer interested callers to smoking cessation groups run by the ACS, the American Lung Association and the American Heart Association; operate a bureau of speakers on cancer prevention available to Hispanic community groups; and generate community outreach programs and cancer prevention messages carried by the local media.

Combining Laboratory and Population Studies

Scientists today can detect carcinogens in an individual's outdoor or indoor environment, and can even measure carcinogens, and sometimes their metabolites, in body fluids.

Once a carcinogen enters a cell, it may be activated by enzymes or detoxified. Chemically, these activities require several reactions inside the cell. The rate at which these reactions occur differs among individuals, because of the characteristics they have inherited and the changes to genes that have occurred since birth. Both genes and environment affect an individual's cancer risk.

Laboratory researchers working to find new ways to predict cancer risk are trying to take advantage of what they are learning about individual differences detectable by molecular biology and biochemistry.

For example, inherited predisposition to cancer can now be identified in some individuals, based on molecular analyses of the DNA in the cells of people with a family history of certain diseases.

While cigarette smoking and certain occupational exposures clearly increase lung cancer risk, not every smoker develops lung cancer. Recently, scientists have begun to look at how much of a role a person's heredity may play in lung cancer risk. For example, people who inherit an enhanced ability to metabolize the antihypertensive drug debrisoquine may be more susceptible to lung cancer. Another clue is that some lung cancer patients have deletions in regions of specific chromosomes or certain patterns of oncogene expression.

Thus, research in cancer prevention is melding the knowledge of scientists working in the laboratory with that of researchers who study patterns of cancer occurrence in specific groups of individuals. The concepts of cancer initiation and promotion provide the intellectual framework for these multidisciplinary studies, which promise new challenges, opportunities and optimism for the future of cancer research and prevention.

Detecting Cancer: The Earlier the Better

Guidelines

Catching cancer before it spreads increases treatment options and improves a patient's chances of survival. The guidelines below have been approved by a number of medical organizations:*

Colorectal Exam: Physicians should make rectal examination a part of the periodic health checkup. Annual tests for blood in the stool should begin at age fifty. Sigmoidoscopy (visualization of the colon with a thin, flexible medical instrument) should be done every three to five years, starting at age fifty. Physicians should identify for special surveillance patients at high risk, including those with a strong family history of colorectal cancer, or with a personal history of polyps, colon cancer, or inflammatory bowel disease.

Breast Exam: Women should do breast self-examination monthly, and breast examination should be part of a periodic health checkup. Beginning at age forty, a woman should have a mammogram every one to two years. At age fifty, annual mammograms are recommended. Women with a personal history of breast cancer are encouraged to have annual mammograms.

Skin Exam: All individuals should examine their skin thoroughly on a regular basis, and primary care physicians should make skin exams part of the periodic health checkup.

Testicular Exam: Physicians should make testicular examination part of the periodic health checkup, and men should do testicular self-examination monthly.

Prostate Exam: Men over forty years old should have an annual prostate examination.

Oral Cavity Exam: An oral exam should be part of the periodic health checkup. Special attention should be given to patients at high risk due to tobacco and alcohol use.

Pap Test: A woman should have a Pap test (microscopic examination of cells scraped from the uterine cervix) at age eighteen or as soon as she is sexually active. The test should be done once a year until three consecutive exams show no signs of disease. After that, Pap tests can be less frequent if the physician approves.

By using mammography to detect breast cancer in the early stages of disease, many deaths could be avoided. But about 46 percent of women age forty and over have never had a mammogram. Over 15 percent do not know what a mammogram is. Mammography is a low-radiation X-ray that allows doctors to detect small tumors in the breast long before they can be felt in a physical exam.

*The American Medical Association, the National Cancer Institute, the American Society of Internal Medicine, the American Urological Association, the American Academy of Dermatology and the American Academy of Otolaryngology. These guidelines also are compatible with those of the American Cancer Society.

Papillomavirus Infection Revealed by Pap Tests

It has been nearly 100 years since scientists suggested a role for a sexually transmitted infectious agent in cancer of the uterine cervix. Until recently, herpesviruses were the chief suspects.

With the advent of recombinant DNA technology, scientists studying Pap tests discovered that some cervical dysplasias—abnormalities that are recognized as precursors to cancer if left untreated—were the result not of herpesvirus infections but of papillomavirus infections.

Slightly larger than the common cold virus, papillomaviruses are now suspect in several cancers, primarily those affecting the genital tract in both sexes.

Papillomaviruses are widespread in nature. More than forty distinct types of human papillomaviruses (HPVs) have been identified. Most are relatively harmless, causing either no problem, or else benign growths like warts and papillomas.

About fifteen types of HPV are linked to genital tract lesions. HPV 6 and 11 are associated with common venereal warts. Another group, including HPV 16, 18 and 33, and occasionally 31 and 35, are found in moderate and severe cervical dysplasia and in cervical cancer.

Each HPV type has a unique sequence of 8,000 pairs of nucleotides making up the circular, double-stranded DNA core of the virus. This specificity enables scientists to make molecular probes that identify each HPV.

Molecular probes for HPV 16, 18 and 33 have also linked these viruses to cancers of the vulva and penis. Other HPVs have been found in cancers of the anal region, the larynx and in the lung cancer cells of a patient with laryngeal papillomatosis.

Cancer is believed to be a rare consequence of infection by a small number of known HPVs. Growing evidence suggests the need for events other than viral infection for cancer to occur. The events, or cofactors, most often suggested are smoking, use of oral contraceptives, concurrent infection with other agents and a breakdown in the immune system.

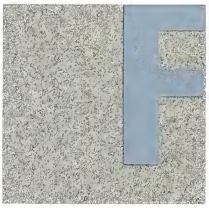
Several groups are conducting studies to pin down the role of HPVs in human cancers, using the tools of recombinant DNA technology. One large study will look at the epidemiology of cervical cancer in 25,000 U.S. women by correlating results of Pap tests, cervical flushes, molecular analyses of HPV infection and subsequent cancer experience.

Because of the close link between certain HPVs and cervical cancer, some scientists are saying the time has come to develop a vaccine against those HPVs most strongly suspected, an effort that would require several years.

Dr. Peter M. Howley,(left) shown here with a coworker, studies the molecular characteristics of papillomaviruses and their role in cancers.

Chemoprevention: A New Frontier In Cancer Prevention

By Anne Rodgers



For years, scientists have known that vitamin A and its derivatives, nutrients found in dark green, deep yellow and orange fruits and vegetables, and in egg yolks and liver, are essential for healthy skin, hair and mucous membranes, and for normal vision. More recently, however, evidence from epidemiologic studies has shown that people with low vitamin A intake or blood levels face higher risks of certain cancers. This has led scientists to look more closely at vitamin A and related substances to see how they affect cancer development and whether they might be used in cancer prevention.

Chemoprevention is the addition of selected synthetic or natural substances into the diet with the goal of reducing cancer risk.

"Whether certain micronutrients can reduce cancer risk is a hypothesis being tested in a number of interesting clinical trials," says Winfred F. Malone, Ph.D., chief of the NCI Chemoprevention Branch.

More than 600 compounds have been identified as having some evidence of ability to interrupt the cancer process. Besides vitamin A, attention has focused on vitamins C and E, the trace element selenium, and calcium.

For research purposes, a compound must undergo rigorous laboratory tests to see if it is safe for people as well as effective in inhibiting the activity of known carcinogens. Because vitamin A in large doses is toxic to the liver, scientists had to find synthetic forms of the vitamin with the same cancer-inhibiting properties but without the toxicity. It was also essential that this synthetic compound reach targeted tissues without accumulating in the liver.

An International Experiment: Using Nutrients to Cut Cancer Rates

The death rate for esophageal cancer in Linxian, a dry and mountainous region near the center of the People's Republic of China, is the highest in the world. Three new cases of esophageal cancer are diagnosed each day, compared to one a month among a comparable number of white Americans, or two a month among black Americans.

In Linxian, poor nutrition seems to play a major role in the development of esophageal cancer; among Americans, cigarette smoking and heavy alcohol use are also suspect.

The NCI and Chinese epidemiologists have interviewed 3,000 of Linxian's inhabitants about their dietary habits; these data are currently being analyzed.

Pilot chemoprevention studies began in 1983, and full-scale trials in 1985. Approximately 3,400 men and women who are known to have precancerous lesions of the esophagus are taking either a multiplicity of vitamins and minerals —a total of twenty-six different substances—or none at all. In another trial, approximately 30,000 villagers who live in this high-risk area are taking various combinations of nine vitamins and minerals.

Dr. Michael Sporn's laboratory at the NCI is studying potential chemo-preventive agents.

It took Dr. Michael Sporn and his colleagues at the NCI five years to test 1,000 analogs of vitamin A, called retinoids. Each week, cultures of hamster tracheas were used to screen retinoids for their ability to suppress the process of carcinogenesis. The scientists looked for retinoids with low toxicity and effective distribution in the tissues. The researchers found a number of compounds with these attributes, including N-(4-hydroxyphenyl)retinamide, or 4-HPR.

The next step was testing 4-HPR in laboratory animals. In a series of studies, Richard Moon and coworkers at the Illinois Institute of Technology Research Institute in Chicago found that 4-HPR was effective in preventing the development of breast cancers in rats treated with the carcinogen nitrosomethylurea. They also found that 4-HPR accumulated only in breast tissue, and did not cause toxic effects at the levels studied.

Dr. Charles Hennekens heads a chemoprevention study with 22,000 healthy physicians.

Based on a careful evaluation of these and other studies, the NCI decided to fund a controlled clinical trial of 4-HPR through Italy's National Cancer Institute in Milan. Under the supervision of Dr. Umberto Veronesi and his colleagues, several thousand women who have had cancer in one breast are taking 4-HPR to see if it will prevent cancer from developing in the other breast. An equal number of women are serving as control subjects. Both groups are being closely monitored with periodic blood tests, chest and bone X-rays and mammograms.

Another promising chemopreventive agent is beta-carotene, a vitamin A precursor that is found mainly in fruits and vegetables. A number of epidemiologic studies have shown lower incidences of cancer associated with high intakes of vegetable and fruits containing beta-carotene. Scientists speculate that beta-carotene may play a role in preventing cancer initiation, the initial damage to a cells' DNA by a carcinogen. It also may act as an antipromoter, reducing the chances that an initiated cell will convert to a cancer cell

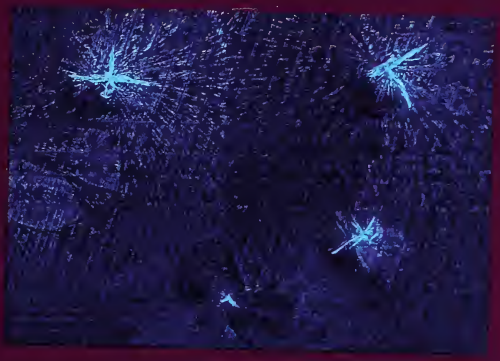
In one study, Dr. Charles Hennekens and his colleagues at Harvard University and Brigham and Women's Hospital in Boston are testing the effects of beta-carotene supplements on future cancer incidence in a group of over 22,000 healthy physicians.

In a second study, Dr. Gilbert Omenn and his colleagues at the Fred Hutchinson Cancer Research Center at the University of Washington School of Public Health in Seattle are testing a combination of vitamin A and beta-carotene in men at high risk for lung cancer because of occupational exposure to asbestos. The study, which includes smokers and nonsmokers, will evaluate the efficacy and safety of these compounds.

Almost twenty chemoprevention clinical trials are now under way. These studies, often collaborations between industry and government-supported researchers, test the appealing hypothesis that diet or dietary supplements, such as vitamins, may some day be used to prevent or inhibit cancer.

Richard Moon led laboratory tests for the safety and efficacy of different dosage levels of 4-HPR, a synthetic retinoid now under test in Italy to see if it will be a useful chemopreventive agent for breast cancer.

SPIN-OFFS



Knowledge does not always accrue in a predictable fashion. Cancer research has in many cases led to basic understandings of other diseases. For instance, a long-used anticancer drug has proven useful in treating a form of arthritis. The search for a viral cause of cancer led to a well established program which not only revealed information about oncogenes, but sped the finding of vital information about the cause of AIDS. Similarly, studies on an oncogene have provided a way of marking a gene postulated to cause cystic fibrosis, and still other studies led to identification of a gene predisposing people to a form of neurofibromatosis.

Dividends of Cancer Research

Like other areas of biomedical research, cancer research sparks spinoff discoveries, providing critical insights into the causes or treatment of diseases other than cancer. AIDS research is the most obvious example: most of the existing scientific knowledge and expertise on retroviruses has come from laboratories that have been supported by the National Cancer Program. Whether by competition or collaboration, cancer research has proved fruitful in several other areas of biomedicine as well. Following are a few examples.

New Test for Diagnosing Cystic Fibrosis

In October 1985, scientists from two competing groups, in the United States and Great Britain, independently reported finding new genetic markers for cystic fibrosis (CF) on chromosome 7. CF is the most common fatal genetic disease, afflicting one in every 2,000 children born in this country. Although improvements in treating the symptoms of CF have allowed most patients to live into their twenties, scientists still have not discovered the exact defect that causes this disease.

In patients with CF, the body produces abnormally thick mucus that clogs the lungs and digestive system, interfering with breathing and digestion.

Patients with CF have inherited a defective gene on chromosome 7 from both parents. Brothers and sisters who do not have the disease have inherited to normal chromosomes or they have inherited one normal chromosome and one chromosome with the defective gene, making them carriers for the disease. Carriers can pass on the genetic defect to their children.

The work on CF inheritance done in this country was a spin-off of cancer research to find a pattern of genetic susceptibility in families with cancer.

Scientists examining genetic variability at the University of Utah and the NCI Frederick Cancer Research Facility (FCRF) discovered that the oncogene *met* is located close to the postulated CF gene, providing an accurate marker for tracing CF inheritance in families. Because of the identification of additional CF markers since 1985, the scientists now have a test that detects CF carriers and patients prenatally in about 70 percent of families with a history of CF. The test is based on detecting genetic variations in the region of the chromosome where the CF gene resides.

Currently, this test can only be used in families with a history of CF. Because the defective CF gene has not yet been isolated, no test is yet available to detect the 10 million Americans, one in twenty, who are symptomless carriers.

AIDS Research

When AIDS was first described in the early 1980s, cancer researchers studying retroviruses already knew that at least one human retrovirus could cause a form of leukemia in humans. Retroviruses are viruses that package their hereditary information in the genetic master chemical called RNA (ribonucleic acid). Besides cancer, retroviruses cause a variety of immune system and neurological disorders in animals.

Scientists searching for signs of retrovirus infection in AIDS patients were soon rewarded with the isolation of a new human retrovirus, now called HIV, or human immunodeficiency virus. Dr. Luc Montagnier of the Pasteur Institut in Paris and the NCI's Dr. Robert C. Gallo, Jr., are credited with co-discovery of HIV. Dr. Gallo also developed the first blood tests for the AIDS virus based on detection of viral antibodies.

Cancer research also has provided drugs to treat AIDS and its related opportunistic infections. AZT (Retrovir), an anti-cancer agent first synthesized in the 1960s, inhibits the activity of HIV in the test tube, and, although not a cure, it prolongs the lives of AIDS patients by reducing the occurrence of life-threatening opportunistic infections. It can also improve the dementia seen in some AIDS patients. Now commercially available by prescription for the majority of AIDS patients, AZT is still being studied, alone and in combination with other drugs. For example, AZT given alternately with dideoxycytidine (ddC), another drug first studied as a possible cancer drug, may be a more effective and less toxic treatment than either drug given alone.

Two other related drugs, dideoxyadenosine (ddA) and dideoxyinosine,

were first synthesized in 1964 as possible cancer drugs but, like AZT, were found ineffective. Now, these drugs too are undergoing patient testing as treatment for AIDS.

In 1987, cancer researchers reported that the anticancer drug trimetrexate, in combination with leucovorin, is an effective treatment for Pneumocystis carinii pneumonia, the opportunistic infection that is a frequent cause of death in AIDS patients.

Other cancer researchers that year developed a new and faster test for detecting and measuring the amount of HIV present in blood cells. This test will speed efforts to find drugs that act against HIV by measuring how well candidate drugs stop the virus from replicating. In the future, the test may also provide physicians with an easier, less expensive and more accurate means of measuring patients' HIV levels.

In addition to basic research and drug development, cancer researchers have been leaders in the search for an AIDS vaccine, as well as in the study of disease risk in groups exposed to the virus.

Gene for Neurofibromatosis Identified. Genetic linkage analysis, a method of pinpointing the chromosomal location of genes responsible for hereditary disorders, has been used widely by cancer researchers studying families predisposed to cancer or benign tumors. In 1987, cancer researchers were among the first scientists to use genetic linkage to dentify chromosome 17 as the location for the defective gene that causes neurofibromatosis 1 (NF-1), the most common form of the disease.

Soon, cancer researchers identified a gene predisposing people to neurofibromatosis 2 (NF-2), a less common form of the disease, on chromosome 22. Finding the defective gene may lead to better prenatal and presymptomatic tests for the neurofibromatoses.

Neurofibromatoses are genetic disorders that result in tumors of the neurological system. NF-1, which afflicts an estimated one in 4,000 people, is characterized by multiple brown or cafe-au-lait spots on the skin, nerve tumors of variable sizes under the skin and curvatures of the spine and other bones. Patients also may have learning disabilities.

NF-2 affects one in 50,000 people. It is characterized by head or spinal tumors masses. These central nervous system tumors often lead to deafness, balance disorders and paralysis.

There is no cure yet for the neurofibromatoses, but surgery and other treatments can reduce the physical signs of these conditions. Early detection may allow for corrective surgery before permanent nerve damage occurs.

Methotrexate in Rheumatoid Arthritis

Although methotrexate, a well-known anticancer drug, was first used to treat rheumatoid arthritis in the early 1950s, its ability to effectively treat this disease was not widely recognized until recently. Now, many physicians use methotrexate in the treatment of rheumatoid arthritis after conventional therapy has failed.

Rheumatoid arthritis is a chronic condition characterized by inflammation of the peripheral joints and consequent destruction of joint structures. Deformities of the affected joints are not uncommon. The condition usually occurs between the ages of 25 and 50. While its exact cause is not known, rheumatoid arthritis is considered one of many autoimmune disorders. These disorders occur when the body begins producing antibodies against its own cells, causing injury to body tissue.

Studies of methotrexate's efficacy in rheumatoid arthritis indicate that the drug reduces swelling and tenderness in joints.

Glossary

adjuvant chemotherapy: The use of one or more anticancer drugs in addition to surgery or radiation therapy as part of the initial treatment of cancer.

antibody: A protein formed by the body's immune system that binds with foreign proteins (antigens) or other large molecules.

autocrine motility factor: A protein that causes some human cancer cells to grow "legs" or pseudopodia that enable them to move to other parts of the body.

autoimmune: When an individual's immune system attacks his or her own tissue.

bases: Chemical compounds that are a critical component of the nucleotides that comprise the backbone of DNA and RNA. The names of the bases—adenine, guanine and cytosine (found in both DNA and RNA); thymine (found only in DNA); and uracil (found only in RNA) are often abbreviated as A, G, C, T, and U, respectively. (These letters are often used in diagrams to represent the nucleotides containing these bases.)

B lymphocytes: White blood cells derived from bone marrow that are involved in production of antibodies.

benign: Not cancer. A benign growth does not invade and spread to other parts of the body.

beta-carotene: A precursor of vitamin A that is found mainly in yellow and orange vegetables and fruits; may be an important lead in chemoprevention.

biologicals: Natural substances produced by living organisms. Examples include interferon, interleukin, colony stimulating factors and monoclonal antibodies. Biologicals are becoming important new tools in the diagnosis and treatment of cancer.

biopsy: The removal and microscopic examination of tissue samples from the living body for diagnosis.

bone marrow: The inner, spongy core of bone that produces blood cells.

bone marrow transplantation: A method of transferring healthy bone marrow cells from a donor to a patient whose bone marrow is unable to produce normal, healthy blood cells.

bronchus: One of the large air passages of the lung.

capillaries: Tiny blood vessels.

carcinogen: Any substance that is known to cause cancer either in animals or in humans.

carcinogenesis: The process of cancer production.

carotenoids: Precursors to vitamin A. One example is beta-carotene, found mainly in fruits and vegetables. Beta-carotene is being studied as a possible chemopreventive agent.

catheter: A thin, flexible tube used to inject fluid into the body or to drain fluid from the body.

cell division: The process by which cells reproduce.

cervical dysplasias: Abnormalities of the cells of the uterine cervix that may be precursors to cancer.

cervical flushes: Washings of the uterine cervix to collect cells for microscopic examination.

chemoprevention: The use of natural and synthetic agents to reduce the incidence of cancer by halting or reversing its development of cancer in people already exposed to carcinogens or potential carcinogens.

chemotherapeutic agents: The medications or drugs used to treat disease.

chemotherapy: Treatment with drugs.

chromosomes: Structures in the cell nucleus that contain the genes.

chromosome staining: The use of a dye to color the chromosomes of a cell to permit detection of abnormalities.

chronic myelogenous leukemia: A form of leukemia involving distorted granulocyte growth.

clinical trials: In cancer research, a clinical trial generally refers to the evaluation of treatment methods, such as surgery, drugs or radiation techniques according to a formal study plan.

clone: The progeny of a single cell or organism created by asexual reproduction.

colon cancer: Cancer of the large intestine.

colony stimulating factor: A growth factor that stimulates maturation of blood cells.

computerized tomography (CT): A scanning procedure that combines X-rays and computer processing to produce a detailed picture of a cross-section of the body in order to detect abnormalities.

controlled studies: Evaluation of new or innovative treatment methods by comparison with standard treatment. In a controlled study, a control group receives the standard treatment or no treatment, while an experimental group receives newly developed treatments.

cosmid: An altered phage used as a cloning vector designed to carry large fragments of DNA.

cryosurgery: A technique in which tissues are exposed to extreme cold, resulting in their destruction.

cutaneous: Pertaining to the skin.

cystic fibrosis: A hereditary disorder of infants, children and young adults characterized by chronic respiratory disease, digestive and metabolic abnormalities, and high levels of salt in the sweat.

diagnostic imaging: Use of X-rays, ultrasound or other scanning methods to visualize internal body structures in order to determine state of health.

disease-free survival: Includes all patients who are free of recurrence of disease.

DNA (deoxyribonucleic acid): The substance of heredity; a large molecule that carries the genetic information necessary for the replication of cells and directs the building of proteins.

drug regimen: Dose and frequency of administration of medication.

drug resistance: The capacity of certain cancer cells to survive and grow in the presence of concentrations of anticancer drugs that would usually be fatal to those cells.

ductal breast cancer cells: Cells from cancers that originate in the milk ducts of the breast.

enzyme: A protein substance that catalyzes or speeds up the chemical reactions of a cell.

epidemiology: The study of the prevalence and spread of disease.

Ewing's sarcoma: A malignant tumor of the bone which is most frequently found in children.

familial adenomatous polyposis (FAP): A rare hereditary condition that shows up in adolescence in which the large intestine is carpeted with hundreds of small growths called polyps. FAP predisposes to colon cancer.

gamma camera: Any one of several nuclear medical scanners.

gene: A unit of heredity located in the chromosomes in the cell's nucleus.

gene marker: A piece of genetic material with a distinctive feature that is easily identified in laboratory testing.

genetics: The study of heredity in cells and organisms.

genome: The entire body of genetic information carried by a cell.

germ cells: The female reproductive cells called ova (eggs) and the male reproductive cells called sperm.

granulocytes: White blood cells that engulf and destroy foreign material.

growth factors: Substances that encourage cells to grow.

hairy cell leukemia: A form of leukemia in which the malignant cell population is made of unusual-appearing cells with numerous fine projections on their surfaces.

hereditary: Genetically transmitted from parent to offspring.

Hodgkin's disease: A form of cancer affecting the lymphatic and other tissues that play a part in the individual's ability to fight infections.

hybridization: Pairing of complementary DNA or RNA molecules.

hybridoma: A cell made by fusing an antibody-producing B lymphocyte with a special laboratory-grown cancer cell.

hyperthermia: An experimental cancer treatment in which heat is used to kill tumor cells.

immune system: The interacting group of cells and substances distributed throughout the lymph and blood that defend the body from foreign substances that might cause infection or disease.

immunoglobulin gene: A gene that directs the production of antibody.

immunology: The study of the immune system.

***in situ* hybridization:** A laboratory technique in which a labeled segment of DNA or RNA pairs with its complementary segment, allowing visualization of the location of DNA on the chromosome or RNA in the cell.

infusion pump: A self-contained pump worn on the belt or on a harness, usually used for chemotherapy infusion. The pump maintains a slow, continuous flow of medication to the body over a designated period of time.

initiation: The consequence of the initial interaction of a cell with a cancer causing agent.

initiator: An agent that causes genetic damage that may start the cancer process.

interferons: Large protein molecules that help activate the body's immune system and also interfere with the growth of viruses.

interleukin-2 (IL-2): A lymphokine that supports growth and differentiation of thymus-derived lymphocytes. Also called T-cell growth factor.

involuntary smoking: The inhalation of tobacco combustion products in a smoke-filled atmosphere by a nonsmoker; also called "passive smoking."

iridium seed implant: The radioactive element, iridium, is inserted at a tumor site to irradiate and kill the tumor cells.

labeling: The process of placing a radioactive atom in a molecule to trace its location by the radiation it emits.

laryngeal papilloma: A benign tumor that projects from the lining of the larynx.

laser surgery: Surgery conducted with a special light beam that can produce intense heat and power when focused at close range.

leukemia: Any cancer of the blood-forming tissues characterized by production of abnormal leukocytes.

leukocytes: White blood cells.

leukoplakias: White patches inside the mouth on the cheeks, gums and tongue that may be precursors to cancer.

lumpectomy: Surgical removal of a cancerous breast lump with little if any adjacent breast tissue.

lymphatic system: A circulatory network of vessels carrying lymph, together with the lymph organs that produce or store cells of the body's immune system.

lymph: An almost colorless fluid composed of excess tissue fluid and proteins found in the body's lymphatic vessels.

lymphocyte: A type of white blood cell that is part of the body's immune defenses.

lymphokines: Powerful substances, produced and released into the bloodstream by T lymphocytes, capable of stimulating other cells in the immune system.

macrophages: Cells other than leukocytes that engulf and destroy foreign materials.

magnetic resonance imaging (MRI): A technique that employs a magnetic field to provide images of the internal structure of the body. A computer creates the images from magnetic frequencies, each of which corresponds to particular structures in unique locations in the body.

maintenance therapy: Treatment designed to keep a patient in remission after initial therapy has eliminated all signs of disease.

malignant: Cancerous; refers to uncontrolled abnormal growth of cells that can invade and destroy healthy tissues.

mammography: A technique for X-raying the breast that reveals tumors before they could be found in a breast physical exam.

melanoma: A malignant tumor originating from cells that produce skin pigmentation.

metastasis: The spread of cancer from its original site to one or more additional body sites.

micronutrients: Essential dietary constituents, such as vitamins and trace minerals, required by the body in small quantities.

modified radical mastectomy: Removal of the breast, breast skin, nipple, areola and underarm lymph nodes; the chest muscles are saved.

molecular biology: The study of structures and processes that occur at the molecular level, especially the large molecules that are the components of living matter.

monoclonal antibodies: Genetically identical molecules used in diagnosis and therapy. The antibodies can be targeted to specific sites in the body and may be mass-produced by hybridoma cells.

mullerian ducts: The embryonic tissue that forms the uterus, fallopian tubes and vagina.

mullerian inhibiting substance (MIS): A substance that binds to the receptors of the mullerian ducts, causing them to shrivel and thereby permit fetal male sex organs to develop.

mutation: An alteration in a gene. A mutation can occur in somatic cells or germ cells, but only a change in germ cells will be transmitted to the offspring.

neuroblastoma: A cancer of the nervous system that affects mostly infants and children up to ten years of age.

neurofibromatosis: Any of various clinically and genetically dissimilar disorders associated with multiple, benign, localized or diffuse tumors of the nervous tissue (called "neurofibromas"). The severity of the condition is extremely variable, and a predisposition for malignancy exists.

neutrophils: White blood cells that fight bacterial infection.

non-Hodgkin's lymphoma: Cancer of the lymphoid tissues (lymphoma) other than Hodgkin's disease, including both nodular and diffuse lymphoma.

nonionizing radiation: Energy absorbed in the form of heat that does not damage tissues; an example is ultrasound.

nuclear medicine: The science of using radioactive nuclides to produce diagnostic images and to treat certain cancers.

nucleotides: Chemically distinct units that combine in precise order to form DNA or RNA.

nucleus: The component of the cell that contains the gene-bearing chromosomes and that controls and regulates the activities of the cell.

oncogene: A modified normal gene whose altered activity allows a normal cell to become cancerous.

oncologist: A physician who is a specialist in treatments for cancer.

opportunistic infection: An infection in immune-suppressed persons caused by organisms that do not usually cause illness in people with normal immune systems.

optic nerve: The nerve that carries impulses for the sense of sight. The second cranial nerve.

osteosarcoma: A bone cancer that occurs most frequently in children.

papillomavirus: A family of viruses that cause papillomas, benign tumors that project from the skin or the lining of an organ or tube. Some are associated with certain cancers.

Pap test: A technique for early detection of cervical abnormalities, including cancer. The test involves microscopic examination of cells from the cervix.

phage: Lambda bacteriophage is a DNA virus which replicates in certain bacteria and is widely used in recombinant DNA technology as a vector to clone DNA inserts as large as 20,000 bases. The foreign DNA is amplified as part of the phage DNA genome during the virus infection cycle.

pharmacology: The study of drugs, including their composition, uses and effects.

photodynamic therapy: Treatment that uses the energy or forces exerted by light to kill tumor cells.

photosensitizer: A chemical that makes selected cells sensitive to light. Used in photodynamic therapy to destroy certain cancer cells.

plasmid: A self-replicating circular DNA molecule that is often used in recombinant DNA techniques as a vector to produce large quantities of small DNA inserts.

positron: A positively charged electron.

positron emission tomography (PET): A scanning procedure that constructs images showing the location within a patient of radionuclides that decay by positron emission. Using labeled molecules such as sugar, PET records specific information about the metabolism of the tissue being scanned.

probe: A radioactively labeled segment of DNA or RNA used to identify and locate complementary DNA or RNA molecules in both viruses and living organisms.

promoter: An agent that advances the development of cancer, once a normal cell has been damaged by an initiator.

prosthesis: An artificial replacement for a missing part of the body, such as an artificial limb or breast form.

proteins: Complex organic compounds, widely distributed in plants and animals, that form the principal constituents of the cell protoplasm. Proteins are required for all life processes.

protocol: The plan for use of an experimental procedure or treatment.

proton beam therapy: The use of high-energy penetrating rays composed of a stream of nuclear particles called protons to treat disease.

pseudopodia: Tentacle-like projections of the protoplasm of certain cells that enable them to move about or take in food.

radical mastectomy: Surgical removal of the breast, underlying chest muscles, lymph nodes under the arm and some fat.

radiation therapy: The use of high-energy penetrating rays to treat disease. Sources of radiation include X-ray, cobalt and radium.

radionuclide: A compound that contains a radioactive isotope. As it disintegrates, the isotope emits small, harmless amounts of radiation that can be picked up on a radionuclide image.

radionuclide imaging: A diagnostic process in which a radioactive compound is injected and its image is displayed on a scanner or gamma camera system. The image obtained from a moving detector is called a scan; the image obtained from a stationary camera device is called a scintophotograph.

rearrangements: Changes in the order in which the genes are located along the chromosome.

receptors: Proteins on a cell's surface that enable it to react to external signals. These signals may be growth factors, hormones, photons of light, nutrients or neurotransmitters. Different cells respond to different hormones and growth factors because they have different receptors.

recombinant DNA technology: Techniques for cutting apart and splicing together pieces of DNA from different organisms.

remission: The decrease or disappearance of the symptoms of a disease, such as cancer. Also the period during which this occurs.

rescue: Avoidance of cell death from a high dose of an anticancer drug by administration of an antidote to that drug.

RNA (ribonucleic acid): A nucleic acid, a universal component of all living cells, that plays an important role in transmitting genetic messages between structures in the cell. It also forms the genetic material of certain viruses.

restriction enzymes: Enzymes that split the DNA molecule across both strands at sites where specific nucleotide sequences are located.

retinoblastoma: A rare eye cancer seen only in children. It is often inherited.

retinoids: Vitamin A and synthetic compounds similar to vitamin A. Synthetic retinoids are under study to see if they have any role in blocking the action of cancer-causing agents.

retrovirus: A class of virus that stores its genetic information as RNA. Retroviruses are implicated in carcinogenesis, AIDS and certain neurologic diseases. The human T-cell leukemia/lymphoma virus is a retrovirus.

sarcoma: A malignant tumor originating in bone, cartilage, muscle, fibrous connective tissue or fatty tissue.

second-line therapy: Treatment following an initial, unsuccessful attempt to achieve remission. Second-line therapy usually involves drugs or combinations of drugs different from those used initially.

sex chromosomes: The pair of chromosomes responsible for sex determination.

smokeless tobacco: Tobacco products used for chewing, dipping or sniffing, such as chewing tobacco or snuff.

somatic cells: Any cell other than a germ (egg or sperm) cell.

Southern blot analysis: A molecular analytic test in which DNA, isolated from cancer or normal cells, is cut into different-sized fragments with a restriction enzyme. These fragments are separated by size on a gelatin slab and then transferred to a solid matrix, where a DNA probe containing the gene or special segment of DNA under study, bonds to the matching portion of DNA on one of the fragments. Because the fragment is radiolabeled, it appears as a dark band when the matrix is exposed to X-ray film.

staging: Tests to determine the extent of disease.

standard regimen: A treatment or other intervention considered to be of proven effectiveness on the basis of past studies.

synergistic: Acting together; referring to an agent capable of acting together with other agents to produce an effect greater than that of the sum of each agent acting separately.

translocation: The repositioning of a piece of a chromosome from its usual site to another in the genome.

T lymphocytes: White blood cells that are processed in the thymus. They produce lymphokines and are responsible, in part, for carrying out the immune response.

ultrasound: A diagnostic technique that bounces high-frequency sound waves off organs and other internal structures and converts the echoes into pictures.

vector: A DNA molecule that can be replicated and amplified in living cells. In DNA cloning, a fragment of DNA is inserted into the vector, so that large quantities of the fragment can be made in order to study it.

virus: One of a group of minute infectious agents that lack independent metabolism and can only replicate within living host cells.

Wilms' tumor: A childhood kidney cancer.

X-ray: High energy radiation used in high doses to treat cancer, or in low doses to diagnose abnormalities.

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Credits

Design:
Miles Fridberg Molinaroli, Inc.

Illustrations:
Jane Hurd

Major photography:
Bill Branson/NIH

Cover:
DNA Foreground:
Mike Mitchell
Cisplatin Background:
Larry Otsby/NIH

Page 05:
Timothy Holt

Page 11:
Mike Mitchell

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Laboratory of Pathology, NCI

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Basic Research Laboratory/Frederick Cancer Research Facility

Page 30:
Larry Otsby/NIH

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Dr. Einhorn:
Rick Baughn/Indiana University

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3-D CT Scan:
Courtesy of
Department of Radiation Oncology/Memorial Sloan-Kettering Cancer Center
Photodynamic Therapy:
Courtesy of
Thomas F. De Laney, M.D./NIH
Proton Beam Therapy:
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Michael Goitein, Ph.D./Massachusetts General Hospital
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Michael Welch, Ph.D./Mallinckrodt Institute of Radiology
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Ultrsound-Ovary:
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Barry B. Goldberg, M.D./Thomas Jefferson University Hospital
Hyperthermia:
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Padmakar Lele, M.D./Massachusetts Institute of Technology
Monoclonal Antibodies:
Courtesy of
Jorge Carrasquillo, M.D./NIH

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Fred Hausheer, M.D./Frederick Cancer Research Facility

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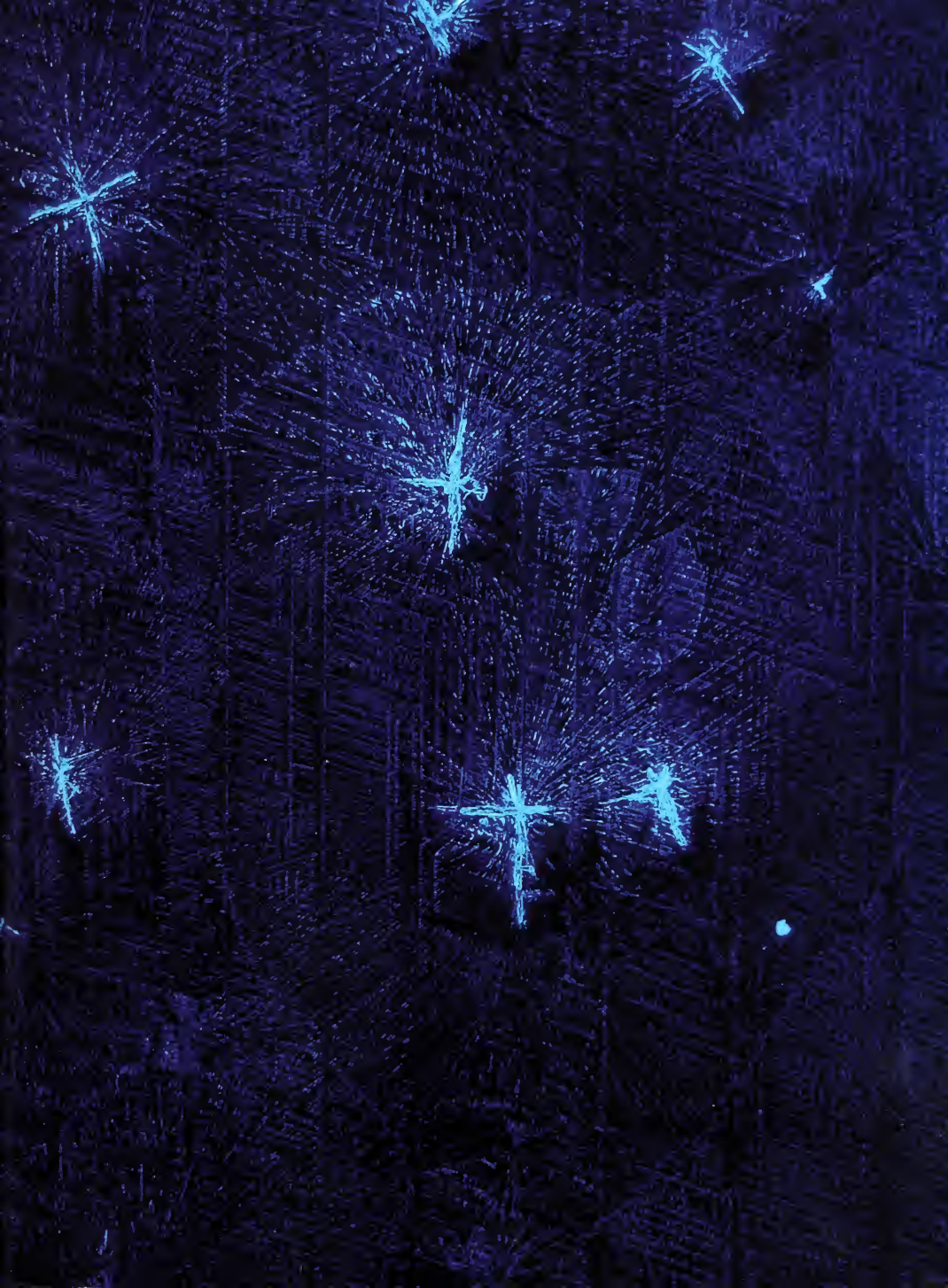

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